Department of Medicine
Division of Nephrology
Helsinki University Central Hospital
Helsinki, Finland

Folkhälsan Research Center
Folkhälsan Institute of Genetics
University of Helsinki
Helsinki, Finland

The impact of the metabolic syndrome and parental risk factors in patients with type 1 diabetes

Lena Thorn

ACADEMIC DISSERTATION

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Supervised by

Docent Per-Henrik Groop
Department of Medicine, Division of Nephrology
Helsinki University Central Hospital

and

Folkhälsan Research Center
Folkhälsan Institute of Genetics
University of Helsinki
Helsinki, Finland

Reviewed by

Docent Leena Moilanen
Department of Medicine
Kuopio University Hospital
Kuopio, Finland

and

Professor Johan Eriksson
Department of General Practice
and Primary Health Care
University of Helsinki
Helsinki, Finland

Opponent

Professor Riccardo Bonadonna
Department of Biomedical and Surgical Sciences
University of Verona
Verona, Italy

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Perfect as the wing of a bird may be, it will never enable the bird to fly if unsupported by the air. Facts are the air of science. Without them a man of science can never rise.
Ivan Pavlov (1849 - 1936)

CONTENTS

ORIGINAL PUBLICATIONS

This thesis is based on the following original publications. The publications are referred to in the text by their Roman numbers.

I Thorn LM, Forsblom C, Fagerudd J, Pettersson-Fernholm K, Kilpikari R, Groop P-H, on behalf of the FinnDiane Study Group. Clustering of risk factors in parents of patients with type 1 diabetes and nephropathy. Diabetes Care 30: 1162-1167, 2007.

I Thorn LM, Forsblom C, Wadén J, Söderlund J, Rosengård-Bärlund M, Saraheimo M, Heikkilä O, Hietala K, Pettersson-Fernholm K, Ilonen J, Groop P-H, on behalf of the FinnDiane Study Group. Effect of parental type 2 diabetes on offspring with type 1 diabetes. Diabetes Care 32: 63-68, 2009.

III Thorn LM, Forsblom C, Fagerudd J, Thomas MC, Pettersson-Fernholm K, Saraheimo M, Wadén J, Rönnback M, Rosengård-Bärlund M, af Björkesten C-G, Taskinen M-R, Groop P-H, on behalf of the FinnDiane Study Group. Metabolic syndrome in type 1 diabetes: association with diabetic nephropathy and glycemic control. Diabetes Care 28: 2019-2024, 2005.

IV Thorn LM, Forsblom C, Wadén J, Saraheimo M, Tolonen N, Hietala K, Groop P-H, on behalf of the FinnDiane Study Group. Metabolic syndrome as a risk factor for cardiovascular disease, mortality, and progression of diabetic nephropathy in type 1 diabetes. Diabetes Care 32: 950-952, 2009.

ABBREVIATIONS

DCCT	The Diabetes Control and Complications Trial
FinnDiane	The Finnish Diabetic Nephropathy Study
HbA_{1c}	Glycosylated hemoglobin A_{1c}
HDL	High-density lipoprotein
HLA	Human leukocyte antigen
LADA	Latent autoimmune diabetes in adults
LDL	Low-density lipoprotein
$MS^{AHA/NHLBI}$	Metabolic syndrome according to the American Heart Association and the National Heart, Lung, and Blood Institute
MS^{EGIR}	Metabolic syndrome according to the European Group for the study of Insulin Resistance
MS^{IDF}	Metabolic syndrome according to the International Diabetes Federation
MS^{NCEP}	Metabolic syndrome according to the National Cholesterol Education Program Adult Treatment Panel III
MS^{WHO}	Metabolic syndrome according to the World Health Organization

ABSTRACT

Background

One-third of patients with type 1 diabetes develop diabetic complications, such as diabetic nephropathy. The diabetic complications are related to a high mortality from cardiovascular disease, impose a great burden on the health care system, and reduce the health-related quality of life of patients.

Aims

This thesis assessed, whether parental risk factors identify subjects at a greater risk of developing diabetic complications. Another aim was to evaluate the impact of a parental history of type 2 diabetes on patients with type 1 diabetes. A third aim was to assess the role of the metabolic syndrome in patients with type 1 diabetes, both its presence and its predictive value with respect to complications.

Subjects and methods

This study is part of the ongoing nationwide Finnish Diabetic Nephropathy (FinnDiane) Study. The study was initiated in 1997, and, thus far, 4,800 adult patients with type 1 diabetes have been recruited. Since 2004, follow-up data have also been collected in parallel to the recruitment of new patients. Studies I to III have a cross-sectional design, whereas Study IV has a prospective design. Information on parents was obtained from the patients with type 1 diabetes by a questionnaire.

Results

Clustering of parental hypertension, cardiovascular disease, and diabetes (type 1 and type 2) was associated with diabetic nephropathy in patients with type 1 diabetes, as was paternal mortality. A parental history of type 2 diabetes was associated with a later onset of type 1 diabetes, a higher prevalence of the metabolic syndrome, and a metabolic profile related to insulin resistance, despite no difference in the distribution of human leukocyte antigen genotypes or the presence of diabetic complications. A maternal history of type 2 diabetes, seemed to contribute to a worse metabolic profile in the patients with type 1 diabetes than a paternal history. The metabolic syndrome was a frequent finding in patients with type 1 diabetes, observed in 38% of males and 40% of females. The prevalence increased with worsening of the glycemic control and more severe renal disease. The metabolic syndrome was associated with a 3.75-fold odds ratio for diabetic nephropathy, and all of the components of the syndrome were independently associated with diabetic nephropathy. The metabolic syndrome, independent of diabetic nephropathy, increased the risk of cardiovascular events and cardiovascular and diabetes-related mortality over a 5.5-year follow-up. With respect to progression of diabetic nephropathy, the role of the metabolic syndrome was less clear, playing a strong role only in the progression from macroalbuminuria to end-stage renal disease.

Conclusions

Familial factors and the metabolic syndrome play an important role in patients with type 1 diabetes. Assessment of these factors is an easily applicable tool in clinical practice to identify patients at a greater risk of developing diabetic complications.

1 INTRODUCTION

Diabetes currently affects more than 240 million people worldwide. If the level of obesity were to remain constant, by the year 2025, this number will reach 380 million, with the greatest increase expected in developing countries [1]. Such a dramatic increase is mainly due to environmental and behavioral factors such as a sedentary lifestyle, overly rich nutrition, and obesity. The majority of individuals with diabetes have type 2 diabetes, although the incidence of type 1 diabetes is also increasing in parallel with the changes in human behavior and lifestyle [2,3]. The health implications of this epidemic are of unrivalled proportions in terms of morbidity, mortality, and resources directed towards managing the complications of diabetes [4]. Many people with diabetes become blind, require amputations, or develop progressive renal impairment, and most of them will eventually succumb to cardiovascular complications [5]. The increase in the prevalence of diabetes has also led to an increase in diabetic complications. The number of patients in renal replacement therapy (dialysis or renal transplant) is expected to rise worldwide to 2 million by the year 2010 [6].

Diabetic nephropathy affects one-third of patients with type 1 diabetes, and there is an incidence peak after 15 to 20 years of diabetes [7], as well as familial clustering of nephropathy [8], suggesting a genetic predisposition. One approach in the search for genes behind diabetic nephropathy is to identify familial risk factors. Several studies have been performed, and the familial traits investigated include hypertension, cardiovascular disease, type 2 diabetes, early mortality, and factors related to insulin resistance. The results of these often underpowered studies have been contradictory, and none of these have examined the combined effect of these traits or the separate impact of maternal and paternal history of the traits.

Patients with type 1 diabetes have a higher prevalence of type 2 diabetes in their families than in the general population [9]. With the rapidly growing epidemic of type 2 diabetes, a family history of type 2 diabetes is anticipated to become more frequent in patients with type 1 diabetes in the future. It is noteworthy that a family history of type 2 diabetes is strongly associated with a genetic predisposition to type 2 diabetes [10]. A family history of type 2 diabetes is also associated with insulin resistance and the metabolic syndrome in offspring without diabetes [11,12]. Data on the consequences of a family history of type 2 diabetes for the patients with type 1 diabetes are, however, limited.

Patients with type 1 diabetes have an increased risk of cardiovascular morbidity and mortality, and this risk is to a large extent explained by the presence of diabetic nephropathy, but even patients without diabetic nephropathy have a 4-fold increased risk compared with subjects without diabetes [5]. The metabolic syndrome is an important risk factor for cardiovascular disease and even for chronic renal disease in the general population and in patients with type 2 diabetes [13,14]. The metabolic syndrome comprises a cluster of cardiovascular risk factors, including insulin resistance, hypertension, dyslipidemia, and impaired glucose regulation. With the worldwide obesity epidemic, the prevalence of the metabolic syndrome is steadily increasing [15], currently present in 25% of middle-aged Finns and 80% of patients with type 2 diabetes [16].

Notably, a Scandinavian study suggests that patients with type 1 diabetes have a higher energy intake of fat than age-matched subjects without diabetes [17], which may promote obesity in these subjects. One would therefore expect that in line with the worldwide obesity epidemic also patients with type 1 diabetes will become more

obese and encounter problems with reduced insulin sensitivity and metabolic abnormalities related to insulin resistance. In patients with type 1 diabetes, insulin resistance has been implicated in the pathogenesis of both micro- and macrovascular complications [18,19], and the other components of the metabolic syndrome also act as risk factors for diabetic complications. No studies exist, however, on the presence and the consequence of such a cluster of risk factors, the metabolic syndrome, in patients with type 1 diabetes.

2 REVIEW OF THE LITERATURE

Type 1 diabetes – epidemiology and pathogenesis

Type 1 diabetes is an autoimmune disease that results from an interaction between genetic and environmental factors. The disease is characterized by loss of function of the β-cells of the pancreatic islets of Langerhans and leads to absolute insulin deficiency. The discovery of insulin in 1921 by Paulescu, and soon thereafter, the first successful administration of exogenous insulin to humans by Banting and Best revolutionized the treatment of diabetes. The incidence of type 1 diabetes varies in children from 0.1 in Venezuela to 64 per 100,000 person-years in Finland, the country with the highest incidence rate in the world [2,20]. The pathophysiology of type 1 diabetes is still not fully understood, but the disease clusters in families. Recent Finnish data show a 43% probandwise concordance of type 1 diabetes in monozygotic twins [21], and the cumulative incidence of type 1 diabetes is 7% by the age of 20 if one of the parents has diabetes, and even higher if the father has diabetes [22]. Of the genes identified, the human leukocyte antigen (HLA) class II genes are associated with the highest risk of type 1 diabetes, confering about 50% of the genetic susceptibility [23]. The HLA region is a complex entity, but the haplotypes DRB1*0401/2/4/5-DQB1*0302 and DRB1*03-DQA1*05-DQB1*02 are associated with the highest risk of type 1 diabetes, whereas DRB1*15-DQA1*0102-DQB1*0602 is the most common among the haplotypes that protect from diabetes [24]. A genetic susceptibility by itself is, however, not enough, requiring also extrinsic factors that alter the immune system to trigger and sustain the development of the disease. Potential factors include viral infections and early exposure to cow's milk proteins [25], as well as birth by Cesarean section, high birth weight, and greater maternal age [26]. Activation of the immune system by triggering factors leads to an inflammatory response, β-cell autoimmunity/insulitis, characterized by the appearance of auto-antibodies [27], gradual loss of β-cells, and eventually clinical disease.

The incidence of type 1 diabetes is rapidly increasing worldwide, and there is a trend towards decreasing age at presentation [28]. In Finland, the incidence rate has doubled between 1980 and 2005, and a steeper increase has been observed since the late 1990s [2]. At the same time, protective HLA genotypes have become more frequent among patients with type 1 diabetes, suggesting that environmental pressure has become more important and that penetrance of the disease is observed despite lower genetic risk [29]. Different theories have been proposed for the increase in the incidence of type 1 diabetes. One theory is the *accelerator hypothesis*, which proposes that the tempo of the β-cell loss is accelerating in modern society due to an increase in body weight, leading to a younger onset and thereby a higher incidence of type 1 diabetes [30]. In line with this, a Swedish study showed that the total incidence of type 1 diabetes has not increased, but the onset of diabetes has in fact shifted towards an earlier age [28]. The increase in incidence of type 1 diabetes seems to correlate with the observed increase in body weight in Finnish adolescents [3], but recent data from Finland suggest that there is in fact a true increase in the incidence, as the incidence of type 1 diabetes is also increasing among 15 to 39-year-olds [31]. Another theory, the *hygiene hypothesis*, suggests that the increase in incidence is explained by improved hygiene, which has led to a decrease in infections during childhood [32]. This theory is supported by the incidence of type 1 diabetes being lower in areas with higher population density and household crowding [33], and the incidence also correlates with the gross national product [34]. In addition, although the high-risk HLA genotypes are equally common among people on both sides of the Finnish-Russian border, the incidence

of type 1 diabetes is 6-fold higher in Finland, where the socioeconomic circumstances are better [35].

Type 2 diabetes – epidemiology and pathogenesis

Type 2 diabetes is characterized by insulin resistance in target tissues and defects in insulin secretion in pancreatic β-cells, both of which result from an interaction between genetic and environmental factors. The prevalence of type 2 diabetes varies between different populations, being approximately 5 to 10% in European populations, 15 to 20% in Hispanic Americans, and above 50% in Pima Indians [36]. The incidence of type 2 diabetes is increasing worldwide, and in the United States, for instance, the incidence has increased from 267 in 1970 to 445 per 100,000 person-years in 1994 in males [37]. In Finland, the register of the Social Insurance Institution showed that 42,000 adults were using antidiabetic medication in 1970, while the number had increased to 135,000 in 2002 [38]. Type 2 diabetes is usually diagnosed in adulthood, but today the incidence is increasing also in adolescents [31]. Type 2 diabetes clusters in families, and in population-based studies the proband-wise concordance in monozygotic twins is 34 to 50% [39,40]. The risk of type 2 diabetes in offspring of a parent with type 2 diabetes is 16 to 35%, and even higher if both parents have diabetes [10,41]. Type 2 diabetes has a slow onset and can go undiagnosed for many years. The metabolic disturbances in the patients range from mild to severe, and therefore, commonly implemented treatments vary from dietary modifications and changes in lifestyle combined with oral hypoglycemic agents to insulin [42,43]. Type 2 diabetes often coincides with obesity and the metabolic syndrome, both of which are also risk factors for type 2 diabetes, alongside lower levels of physical activity [44,45]. Of the measurements of obesity, waist circumference seems to be the best predictor of type 2 diabetes, followed by the waist-to-hip ratio and the body mass index [46].

Decreased insulin action in the target tissues, including muscle, liver, and adipose tissue, is a central feature of type 2 diabetes and is observed already years before disease onset. Defective insulin secretion also plays an important role and is thought to be the factor driving disease onset [47,48]. Insulin resistance results from a combination of genetic and environmental factors and is closely associated with obesity, age, high-caloric diet, and lack of exercise [48]. The development of β-cell dysfunction occurs early in the disease process [49] and is first characterized by a decreased first-phase insulin response to glucose, which leads to postprandial hyperglycemia and reflective hyperinsulinemia. Although the pathogenesis is not yet entirely clear, glucose toxicity, lipotoxicity, and β-cell exhaustion are factors thought to play a role in the initiation of β-cell dysfunction, and consequently, to lead to inadequate responsiveness of the β-cells to glucose and even loss of β-cell mass by apoptosis [48].

Impact of family history of type 1 and type 2 diabetes

Type 1 and type 2 diabetes aggregate in the same families, suggesting that these two entities could share a common background. Compared with the general population, patients with type 1 diabetes have more type 2 diabetes in their families [9,50], and type 1 diabetes is more frequent in families of patients with type 2 diabetes [9,51]. Both parental type 1 and type 2 diabetes increase the risk of type 1 diabetes in siblings of probands with type 1 diabetes [52]. In line with this, the *accelerator hypothesis* suggests that type 1 and type 2 diabetes in fact represent a disease continuum where the rate of β-cell loss in addition to different genetic susceptibility determine the disease presentation [30].

In patients with type 2 diabetes, a family history of type 1 diabetes, compared with a family history of type 2 diabetes, is associated with a higher prevalence of high-risk HLA genotypes and a lower body mass index [53]. In patients

with type 1 diabetes, first-degree relatives show clustering of other autoimmune disorders, the most common being autoimmune thyroid disease [54]. The effect of maternal and paternal type 1 diabetes might differ since an excess paternal transmission of type 1 diabetes has been observed [22,51].

Nondiabetic first-degree relatives of patients with type 2 diabetes are insulin resistant and have an impaired insulin secretion [11], especially if microalbuminuria is present [55]. In addition, compared with subjects without a family history of diabetes, they show components of the metabolic syndrome [12], vascular dysfunction [56], and chronic low-grade inflammation [57]; all important in the pathogenesis of the metabolic syndrome, type 2 diabetes, and complications of diabetes. Evidence suggests that the effect of a maternal and a paternal history of type 2 diabetes may differ. First, an excess maternal transmission of type 2 diabetes has been reported in many studies [58,59], and second, the metabolic consequences observed in offspring of parents with type 2 diabetes seem to vary according to whether it is the father or the mother who has type 2 diabetes [60,61]. Data on the consequences of a family history of type 2 diabetes on offspring with type 1 diabetes are scarce. Some support for an effect of type 2 diabetes is provided by the Diabetes Control and Complications Trial (DCCT), where improvement in glycemic control in the intensive treatment arm led to an increase in weight gain and triglyceride concentrations, particularly in those with a positive family history of type 2 diabetes [62].

Other forms of diabetes

In addition to type 1 and type 2 diabetes, other forms of diabetes exist. Latent autoimmune diabetes in adults (LADA) resembles both type 1 and type 2 diabetes and shares genetic features with both [63]. Whether classification of LADA as a distinct entity has any clinical value has been questioned [64], although some authors strongly argue for the categorization of subtypes of diabetes [65].

Idiopathic type 1 diabetes, also called type 1B diabetes, is a strongly inherited form of diabetes predominantly observed in subjects of Asian or African origin. It does not involve autoimmunity, and the need for insulin therapy varies between episodes. Maturity onset diabetes of the young (MODY) results from monogenetic defects in β-cell function, has an early age at onset, and is inherited in an autosomal dominant pattern. Other monogenetic forms of diabetes include mutations in mitochondrial DNA causing deafness and diabetes. Also diseases of the pancreas, for instance pancreatitis or pancreas cancer, can cause diabetes by destruction of pancreatic tissue. Moreover, some drugs, such as glucocorticoids, can influence glucose metabolism, impairing insulin action in target tissues [66].

Diabetic complications

Diabetes can result in chronic diabetic vascular complications in both patients with type 1 and type 2 diabetes. Complications related to other forms of diabetes will not be covered in this thesis. The vascular complications can be divided into microvascular and macrovascular complications. Microvascular complications affect the small vessels of the body, especially in the kidneys (nephropathy), retina of the eyes (retinopathy), and the nerves (neuropathy). Macrovascular complications affect the large vessels, for instance the coronary, cerebral, and peripheral arteries. The diabetic complications are strongly associated with the excess mortality observed in patients with diabetes [67], and also result in a great burden on the health care system [4], and most importantly, a reduction in patient's health-related quality of life [68,69]. The following sections include a review of diabetic complications, with the main focus on nephropathy and macrovascular disease in patients with type 1 diabetes.

Nephropathy

Characterization of diabetic nephropathy and renal function

The first clinical sign of diabetic nephropathy is an increased urinary albumin excretion rate in the range of ≥20<200 μg/min, or ≥30<300 mg/24-hours, called microalbuminuria [70]. Below this range, the albumin excretion rate is classified as normal, and if ≥200 μg/min or ≥300 mg/24-hours, considered as macroalbuminuria or overt diabetic nephropathy.

Renal function can be directly measured as the plasma clearance of inulin or exogenous markers, such as ^{51}Cr-EDTA. This is, however, complex and expensive, and thus, not feasible in routine clinical practice, estimates have therefore been developed for the assessment of glomerular filtration rate. The most widely used method is the Cockcroft-Gault formula for estimated creatinine clearance [71], adjusted for body surface area. The more recent Modification of Diet in Renal Disease formula was developed to estimate creatinine clearance in patients with chronic renal disease [72]. Of these two, the Cockcroft-Gault formula is more accurate in the normal and upper-normal range of glomerular filtration [73], while the Modification of Diet in Renal Disease formula seems to be more accurate in patients with chronic renal disease. Both are estimates of creatinine clearance and not specifically glomerular filtration. Creatinine clearance generally overestimates the glomerular filtration because of the tubular secretion of creatinine. Serum cystatin C has therefore been suggested as a new tool to measure renal function, and it seems to be superior to the creatinine-based formulas in detecting a decline in renal function [74]. Renal function is classified based on glomerular filtration rate into normal ≥90, mild decrease in renal function 60 to 89, moderate decrease in renal function 30 to 59, severe decrease in renal function 15 to 29, and renal failure <15 ml/min/1.73 m^2 [75].

Epidemiology

Diabetic nephropathy is characterized by elevated blood pressure, proteinuria, and often a relentless decline in renal function, and its presence is associated with a high cardiovascular morbidity and early mortality [5]. Diabetic nephropathy is the most common cause of renal replacement therapy in the Western world [76]. One-third of patients with type 1 diabetes will develop diabetic nephropathy [7,77], and in a recent Finnish study, after 30 years of diabetes, 8% had developed end-stage renal disease. Notably, in this study, the prognosis of patients with diabetic nephropathy had improved during the past four decades, and children diagnosed with type 1 diabetes before the age of five had the most favorable prognosis [78]. It is evident that not only the incidence of end-stage renal disease, but also the overall incidence of diabetic nephropathy has decreased in patients whose diagnosis of type 1 diabetes has occurred more recently [79,80], due to improved treatment and earlier detection of nephropathy.

Pathogenesis

Diabetic nephropathy is characterized by glomerulosclerosis of the kidney, which leads to leakage of proteins into the urine and a reduction in the glomerular filtration rate. Early in the disease process, glomerular hyperfiltration occurs due to increased capillary pressure in the glomeruli, but further morphologic changes contribute to decreased glomerular filtration [81]. Such changes include mesangial expansion, increased permeability of the glomerular endothelial cells, thickening and decreased negative charge of the basement membrane, and hypertrophy, detachment, and apoptosis of the podocytes [82].

For the development of diabetic nephropathy, the diabetic milieu is a prerequisite, but how the hyperglycemia induces damage to the vasculature is not fully understood. Oxidative stress has been proposed as the unifying factor behind the following four main molecular mechanisms through which hyperglycemia is thought to cause vascular damage [83]: 1) Activation of the polyol pathway, which is a relatively inactive pathway at normal glucose concentrations, leads to conversion of glucose to sorbitol by aldose re-

ductase, which again leads to reduced NADPH and glutathione availability, contributing to intracellular oxidative stress. 2) The irreversible nonenzymatic reaction of reducing sugars and proteins leads to formation of advanced glycation end-products, which can alter the function of the proteins, cause generalized cellular dysfunction, and bind to specific receptors, generating reactive oxygen species. 3) Hyperglycemia also increases protein kinase C activity, leading to activation of growth factors and decreased endothelial nitric oxide synthase activation. 4) Increased activity of the hexosamine pathway due to hyperglycemia causes, for example, increased gene expression of growth factors, such as transforming growth factor β-1.

Oxidative stress is thought to result in endothelial dysfunction, which precedes albuminuria in patients with type 1 diabetes [84], and accordingly, glomerular endothelial dysfunction as well as insulin resistance have been suggested to initiate the cascade that leads to diabetic nephropathy [85,86].

The increased intraglomerular pressure caused by the constriction of efferent glomerular arterioles is thought to result from an activation of the renin-angiotensin system. This system is a major player in blood pressure control and fluid homeostasis. Renin converts angiotensinogen to angiotensin I, which is further converted to angiotensin II by angiotensin-converting enzyme. Angiotensin II is thought to be the key promoter of vascular damage through its actions via angiotensin type 1 receptor. How and why the renin-angiotensin system is activated are unknown, but hyperglycemia *per se* seems to increase renin activity [87], and the renin-angiotensin system is also activated by inflammatory cytokine interleukin-6 [88]. Specific inhibitors of the renin-angiotensin system are effective in the treatment of diabetic nephropathy [89].

Other factors involved in the pathogenesis of diabetic nephropathy include activation of growth factors, such as transforming growth factor β-1, connective tissue growth factor, growth hormone, insulin-like growth factor-1, and vascular endothelial growth factor. These factors contribute to the formation of fibrotic changes in the mesangium and the interstitium, glomerular hypertrophy, and dysfunction of glomerular endothelial cells [85]. Activation of inflammatory cytokines, such as interleukin-1, interleukin-6, and tumor necrosis factor α, is also involved in the pathogenesis of diabetic nephropathy [90].

Risk factors

Microalbuminuria. Microalbuminuria can be viewed as both a marker and a risk factor for diabetic nephropathy. Screening for microalbuminuria identifies patients with incipient diabetic nephropathy and is an effective tool for detecting risk of overt disease [91], although some patients with normal albumin excretion rate also show diabetic renal lesions [92]. Normal albumin excretion is associated with a 17% cumulative incidence of microalbuminuria over 5 to 10 years in patients who have had type 1 diabetes for at least 7 years. Early studies suggested an 80% risk of progression from microalbuminuria to macroalbuminuria [93-95], while more recent data indicate that the risk is approximately 30% over 5 to 10 years [96,97], while in those with diabetes duration of less than 15 years the risk seems to be higher, around 45% [98]. Regression of the albumin excretion rate also occurs. Regression from macroalbuminuria to microalbuminuria, or from macroalbuminuria to a normal albumin excretion rate, is observed in 20 to 30% of patients during follow-up [96,97], and some studies even indicate a greater regression rate [99]. It is noteworthy that microalbuminuria in type 2 diabetes is also associated with similar progression rates to macroalbuminuria as in type 1 diabetes [97], but the structural changes in the kidneys vary considerably, and only 30% of patients with type 2 diabetes and microalbuminuria present with typical diabetic glomerulopathy [82,97]. The strongest risk factors for onset or progression of microalbuminuria include an increase in albumin excretion within the normal range and poor glycemic control along with disease duration [100].

Genetic predisposition. Strong evidence suggests that diabetic nephropathy results from an interaction between susceptibility genes and the diabetic milieu [101]. The incidence peak occurs 15 to 20 years after onset of diabetes, and thereafter the risk declines [7,102], indicating that not all patients with type 1 diabetes will develop nephropathy. Diabetic nephropathy clusters in families of patients with type 1 [8,101,103] and type 2 diabetes [104-106], and in specific ethnic groups [107-109]. In patients with type 1 diabetes, Seaquist *et al.* showed that 83% of siblings of probands with diabetic nephropathy had diabetic nephropathy, whereas the prevalence was only 17% in siblings of probands without diabetic nephropathy [8].

Studies on familial factors in diabetic nephropathy in type 1 diabetes are summarized in Table 1. A family history of hypertension has been associated with diabetic nephropathy in many studies [110-119], suggesting that a genetic predisposition to hypertension is linked to an increased risk of diabetic nephropathy. Not all studies, however, support this finding [120-124]. Since patients with type 1 diabetes and diabetic nephropathy have a several-fold increased risk of cardiovascular disease, genetic factors that contribute to an increased risk of cardiovascular disease could theoretically also explain some of the risk of diabetic nephropathy. A parental history of cardiovascular morbidity and mortality has accordingly been associated with

Table 1. Parental factors associated with diabetic nephropathy in type 1 diabetes

	n	Mean age	HT	DM2	DM1	CVD	Mort	IR
Viberti 1987 [110]	34	27	+				–	
Krolewski 1988 [119]	89	30	+					
Jensen 1990 [120]	98	28	–	–				
Walker 1990 [132]	40	31	+/–					
Nørgaard 1991 [127]	112	30		–		–	–	
Barzilay 1992 [112]	162	29	+					
Earle 1992 [125]	122	42				+	+	
Molitch 1993 [121]	715	27	–					
Yip 1993 [129]	18	42	+/–					+
Freire 1994 [113]	42	13	+					
DeCosmo 1997 [114]	62	35	+	–		+	+/–	+
Erbey 1998 [128]	658	33		+				
Fagerudd 1998 [115]	146	37	+	+		–		
Roglic 1998 [116]	3,250	33	+	+				
Rudberg 1998 [117]	300	20	+	–	–	+/–		
Fagerudd 1999 [118]	137	42	+	+	–		+	
Lindsay 1999 [126]	236	42					+	
Verhage 1999 [123]	57	32	–	–		–	–	–
Campos-Pastor 2000 [119]	312	32	+					
Tarnow 2000 [122]	326	41	–	–		+/–	+	
Fagerudd 2003 [131]	82	38						–
Hadjadj 2004 [130]	275	41	+/–	+/–				+
Harjutsalo 2004 [124]	1,153	-	–	+				
Hadjadj 2007 [134]	160	42	–	+		+/–		
Monti 2007 [322]	4,389	34		+	–			

HT =hypertension, DM2 = type 2 diabetes, DM1 = type 1 diabetes, CVD = cardiovascular disease, Mort = early overall mortality or mortality from cardiovascular disease, IR = insulin resistance, DN = diabetic nephropathy

a higher prevalence of diabetic nephropathy [114,118,122,125,126], and also an increase in cardiovascular disease among patients with diabetic nephropathy [125]. However, many studies show contradictory results [115,123,127]. In addition, family history of insulin resistance and type 2 diabetes has been associated with diabetic nephropathy in some but not all studies [114-118,120,122-124,127-131]. Many of these studies on familial risk factors have been small and have had insufficient power to evaluate the effect of maternal and paternal risk factors separately. Furthermore, whether a clustering of risk factors in parents increases the risk for diabetic nephropathy in offspring with type 1 diabetes is unclear.

Several candidate gene studies have been performed in the search for susceptibility genes for diabetic nephropathy. These studies have, however, often been carried out in a relatively small number of patients, and have generated many positive associations that other studies have been unable to replicate. Interesting genes recognized by this approach include the angiotensin-converting enzyme insertion/deletion polymorphism that was associated with diabetic nephropathy in a large meta-analysis [133], and this association was later confirmed in a European study of patients with type 1 diabetes [134]. Another potential susceptibility gene, the UNC13B, was recently identified, and also replicated in an independent population. This gene is upregulated by hyperglycemia and mediates apoptosis in glomerular cells [135]. A genome-wide linkage analysis of Finnish patients with type 1 diabetes suggested that there is a locus for diabetic nephropathy on chromosome 3q [136]. Further fine-mapping and analysis of this region yielded a significant association with a novel endothelium enhancer, and this finding was replicated in several populations [137]. Genome-wide association studies enable the search for genes involved in pathways not yet recognized in the pathogenesis of the specific disease. Such work is ongoing in several laboratories, and recently, two novel candidate loci were identified by this approach, including loci near the FRMD3 and CARS genes [138].

Glycemic control. Glycosylated hemoglobin A_{1c} (HbA_{1c}) is the most widely used measure of glycemic control, reflecting the lifespan of hemoglobin, and thus, the glucose exposure over the past 2 to 3 months [139]. The beneficial effect of improved glycemic control for diabetic nephropathy was shown in early intervention studies, such as the Kroc Collaborative Study, the Steno Study, the Oslo Study, and the Stockholm Diabetes Intervention Study [140-143]. These studies had a rather low number of patients followed over a relatively short time, and therefore, the final evidence was not provided until results from the large DCCT were published [144]. The DCCT randomized patients with type 1 diabetes, short duration of diabetes, and no signs of microvascular complications into intensive and conventional insulin therapy. During 6.5 years of follow-up, intensive treatment resulted in significantly improved glycemic control compared with conventional treatment (mean HbA_{1c} 7% vs. 9%). Intensive compared with conventional insulin therapy resulted in a 39% reduction in the incidence of microalbuminuria and a 54% reduction in the incidence of overt diabetic nephropathy [144]. Eight years after the closure of the DCCT, the glycemic control between the two groups of insulin therapy were similar (HbA_{1c} 8%), but the beneficial effect of intensive therapy on the development of diabetic nephropathy was sustained, with a 59% reduction in the incidence of microalbuminuria and 84% reduction in the incidence of overt nephropathy [145]. These results suggest that lifetime exposure of hyperglycemia and glycemic memory is important in the pathogenesis of diabetic nephropathy. The beneficial effect of good glycemic control is further highlighted by the reassuring findings of persistent normoglycemia 10 years after simultaneous renal and pancreas transplantation, which resulted in reversal of diabetic renal lesions in a small group of eight patients [146]. Although this approach is not feasible in larger patient cohorts, it highlights the importance of good glycemic control even at this late stage of renal disease.

Hypertension. Type 1 diabetes is associated with hypertension, also in patients without renal involvement, compared with subjects without diabetes [147]. In patients with type 1 diabetes, diabetic nephropathy is clearly associated with hypertension. Hypertension both parallels [148,149] and precedes [150,151] the worsening of renal disease. Accordingly, aggressive treatment of hypertension improves the prognosis of patients with diabetic nephropathy [152,153], especially with the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers with beneficial effects beyond blood pressure-lowering effects [154,155]. For diagnosis of hypertension, most studies have used office blood pressure measurements, which do not reflect the daily variation in blood pressure levels. Accordingly, 24-hour ambulatory blood pressure measurements are more sensitive in identification of patients at risk. Patients with diabetic nephropathy show an absence of the normal dip in nocturnal blood pressure, which may reflect dysfunction of the autonomic nervous system [156].

Dyslipidemia. Dyslipidemia in patients with type 1 diabetes is associated with poor glycemic control, hypertension, and obesity [157], and parallels the worsening of renal disease [157-159]. Lipid abnormalities have even been suggested to be more closely linked to microvascular than macrovascular complications in type 1 diabetes [160]. Patients with type 1 diabetes have elevated high-density lipoprotein (HDL)-cholesterol [161] due to the stimulating effect of insulin on lipoprotein lipase activity [162]. Low HDL-cholesterol and elevated triglycerides, both components of the metabolic syndrome, are associated with abdominal obesity in patients with type 1 diabetes [163]. Few studies have addressed the role of lipids in the progression of renal disease. Mulec *et al.* showed total cholesterol, triglycerides, and apolipoprotein B to be risk factors for progression of renal disease in a small study [164], while regarding the development of renal failure, no effect was observed for triglycerides and total cholesterol in a larger study [150]. Data from our own group suggest that different lipid abnormalities are involved at different stages of progression. Low-density lipoprotein (LDL)-cholesterol was associated with progression to microalbuminuria, while triglycerides predicted progression to macroalbuminuria [165].

Obesity. Obesity has been pointed out as one of the risk factors for the development of end-stage renal disease in the general population [166]. Interestingly, in patients with type 1 diabetes, abdominal obesity has also been linked to the risk of diabetic nephropathy. Waist-to-hip ratio was one of the factors predicting development of microalbuminuria in a 7-year follow-up in the EURODIAB Prospective Complications Study [167], and a 10-cm greater waist circumference at the DCCT closeout was associated with a 1.34-fold increased risk of microalbuminuria over 6 years of follow-up [168]. In addition to the potential role of obesity in the development of microalbuminuria, body weight has been implicated in the development of macroalbuminuria [169]. Interestingly, compared with subcutaneous fat, intra-abdominal fat, which is related to atherogenic dyslipidemia in patients with type 1 diabetes [170], seems to be more strongly related to albuminuria [171].

Insulin resistance. Insulin resistance is observed in patients with type 1 diabetes of varying duration and is associated with poor glycemic control and increased body weight [172,173]. The insulin resistance in type 1 diabetes is reflected in peripheral tissues as well as in increased hepatic glucose production [174]. Using the euglycemic hyperinsulinemic clamp technique, the golden standard for the measurement of insulin sensitivity [175], patients with microalbuminuria have been shown to be insulin resistant [176], and insulin resistance to precede the development of microalbuminuria [177]. Another study found no association between insulin sensitivity and albumin excretion rate [178]. This measurement is, however, complex, time-consuming, and invasive, and therefore, a surrogate estimate of the glucose disposal rate has been developed [179]. Using this surrogate estimation, insulin

resistance has been shown to predict overt diabetic nephropathy in a large cohort [18]. The insulin dose adjusted for body weight can also be used as a surrogate marker of insulin sensitivity in subjects on insulin therapy [180]. The insulin dose correlates negatively with the estimated glucose disposal rate (r = -0.48) [179], but insulin dose does not seem to be a good predictor of progression of renal disease [167,169,177]. Interestingly, pharmacological treatment of insulin resistance with thiazolidinediones seems to have beneficial effects beyond glycemic control and reduces microvascular complications, at least in patients with type 2 diabetes [181]. Taken together, these data favor the view that insulin resistance not only parallels but also precedes the development of diabetic nephropathy in patients with type 1 diabetes.

Other factors. Many other factors have also been shown to increase the risk of diabetic nephropathy. Male gender seems to be associated with increased risk [7], along with smoking [182] and advanced glycation, expressed as limited joint mobility [183] and plantar fascia thickness [184]. Diabetic nephropathy is further associated with chronic low-grade inflammation [185]. The predictive risk associated with markers of inflammation is, however, less clear [186,187], although markers of inflammation are strongly related to endothelial dysfunction [188], which is a risk factor for diabetic nephropathy and decline in renal function [84,186,187].

Retinopathy

Diabetic retinopathy is the leading cause of blindness in the Western world. With effective screening and treatment, an estimated 90% of visual loss can be prevented [189]. The severity of diabetic retinopathy is classified based on the Early Treatment Diabetic Retinopathy Study severity scale into different stages of nonproliferative and proliferative retinopathy. Nonproliferative retinopathy is observed in almost all, whereas the sight-threatening proliferative retinopathy is seen in 15 to 50%, of patients with type 1 diabetes after 15 to 20 years of diabetes [190,191]. Early changes in the retina include microaneurysms, intraretinal hemorrhage, and cotton wool spots, whereas proliferative retinopathy is characterized by ischemia-induced neovascularization of the retina. These new vessels tend to bleed, thereby causing vitreous hemorrhage. Neovascularization can also occur elsewhere, for example in the trabecular meshwork, resulting in neovascular glaucoma [192]. Diabetic macular edema leads to thickening of the retina in the macular region, causing major threat to vision. Macular edema is observed in 10 to 15% of patients with type 1 diabetes after 15 years of diabetes [191].

Diabetic retinopathy, especially proliferative retinopathy, clusters in families [193,194], indicating a genetic predisposition. Diabetic retinopathy often coincides with other diabetic complications, particularly diabetic nephropathy. The severity of diabetic retinopathy is associated with the severity of glomerular morphologic changes [195] and also with the severity of clinical nephropathy [194]. The DCCT showed a beneficial effect of intensive treatment of hyperglycemia on the development of diabetic retinopathy [144], and the effect sustained even after the intensive therapy ended, although the glycemic control worsened [196]. In addition to the classic risk factors for retinopathy, duration of diabetes and poor glycemic control, factors related to insulin resistance have been shown to increase the risk of retinopathy [197]. Screening for diabetic retinopathy by regular fundus photography or ophthalmoscopy plays a key role in the identification of patients at risk. Good glycemic control is essential for the treatment of diabetic retinopathy, as is the treatment of hypertension and dyslipidemia. Retinal laser photocoagulation is needed in cases with severe proliferative retinopathy and macular edema to improve the visual prognosis of patients [192].

Neuropathy

Diabetic neuropathy is the most common cause of neuropathies worldwide, and sensorimotor polyneuropathy starting from the most distal end of the feet and extending proximally with time is the most predominant form of diabetic

neuropathy. The longest nerve fibers are first affected, through both degeneration of axons and demyelination [198]. Symptoms include numbness, burning sensation, stabbing pain, loss of thermal sensation, loss of vibratory sensation, and loss of proprioception, and can result in painless trauma, for example chronic foot ulcers and Charcot arthropathy. Poor glycemic control and duration of diabetes are risk factors for diabetic neuropathy. Hyperglycemia is thought to damage the nerves at least via advanced glycated end-products [199]. No effective cure exists for this irreversible complication of diabetes, and therefore, primary prevention through good glycemic control [144] is the most important goal. Regular clinical foot examination and patient education are necessity in the secondary prevention of chronic foot ulcers.

Autonomic neuropathy is observed in approximately 20% of asymptomatic patients with diabetes. Dysfunction of the autonomic nervous system can be life-threatening, especially when the cardiac autonomic nervous system is affected. Autonomic neuropathy is associated with silent myocardial ischemia and increased mortality. Findings of autonomic neuropathy include resting tachycardia, exercise intolerance, postural hypotension, gastroparesis, atonic bladder, and impotence [200].

Another less common form of diabetic neuropathy is focal and multifocal neuropathy, which mainly affects older patients with type 2 diabetes. This form of neuropathy has a rapid onset and spontaneous recovery, and the pathogenesis includes both inflammation and nerve ischemia. Around 20% of patients with concurrent diabetes and neuropathy present with other neuropathies than diabetic neuropathies, the most common being chronic inflammatory demyelinating neuropathy and pressure palsy, such as carpal tunnel syndrome [198].

Macrovascular complications

Epidemiology

Macrovascular disease in type 1 diabetes has been investigated to a far lesser extent than microvascular complications, although type 1 diabetes is associated with a significant and high risk of cardiovascular disease [201,202], especially in patients with diabetic nephropathy [5,201,203,204]. Limited data on cerebrovascular disease and peripheral vascular disease exist in patients with type 1 diabetes, and in many cases the results are pooled to a common cardiovascular end-point. Thus, the following section reviews the literature on macrovascular disease, with the main focus on coronary heart disease, and presents data on other macrovascular complications when available and appropriate.

Cardiovascular disease is observed in 25% of middle-aged patients with type 1 diabetes [205], and early studies suggest that compared with subjects without diabetes, mortality from cardiovascular disease is 2 to 7 times higher in patients with type 1 diabetes [67,203]. In patients with type 1 diabetes without diabetic nephropathy, the risk of cardiovascular mortality is 4 times higher than in the general population, and the presence of diabetic nephropathy adds to the risk 9 to 10 times, compared with the absence of diabetic nephropathy [5,206]. Recent data show in patients with type 1 diabetes 9 and 42 times higher standardized mortality ratios from ischemic heart disease in males and females aged under 40 years, respectively, and 4 and 7 times higher mortality in those above 40 years [202].

Although the incidence of diabetic nephropathy is decreasing, the incidence of cardiovascular disease shows no trend towards decline [207]. The cardiovascular disease observed in patients with type 1 diabetes shows some disparities compared with that observed in the general population. The protective effect of female gender is not observed in type 1 diabetes, consequently leading to higher standardized incidence and mortality rates in females [202,208,209]. In addition, asymptomatic myocardial ischemia is a common finding in patients with type 1 diabetes [210], especially in patients with diabetic nephropathy [211]. Furthermore, with the same symptoms, patients with type 1

diabetes have a more severe coronary artery disease [212] and the atherosclerosis occurs earlier and is more diffuse [213].

Pathogenesis

Cardiovascular disease results from atherosclerosis, which is characterized by accumulation of lipids and fibrous elements in the walls of the large arteries. Hyperglycemia activates different molecular pathways that lead to intracellular oxidative stress, as discussed earlier regarding diabetic nephropathy [83]. The formation of reactive oxygen species, in addition to hypertension and altered lipoproteins, then leads to endothelial dysfunction, which again results in vasoconstriction, as well as pro-inflammatory and pro-thrombotic changes, contributing to plaque development. Endothelial dysfunction activates adhesion molecules and chemotactic factors, leading to adhesion and penetration of monocytes into the arterial media, where they differentiate into macrophages. Lipids then accumulate intracellularly and cause lesions called fatty streaks. Smooth muscle cells migrate from the media to the intima of the vascular wall, where they proliferate in response to growth factors to form the fibrous cap of the atherosclerotic plaque. A large lipid core and thin fibrous cap predispose to plaque rupture, while the presence of a thick fibrous cap marks a more stable plaque. Myocardial infarctions and other acute clinical events are usually caused by plaque rupture and thrombosis. [214]

Risk factors

Microalbuminuria. As mentioned earlier, diabetic nephropathy is by far the strongest risk factor for cardiovascular disease in patients with type 1 diabetes. Importantly, even a slightly increased albumin excretion rate, both in the normal range [215] and in the range of microalbuminuria [216], predicts atherosclerotic vascular disease. Microalbuminuria is also a potent risk factor for cardiovascular disease in the general population and in patients with type 2 diabetes [217], and thought to reflect a more generalized vascular damage, and not only an increased risk for diabetic nephropathy [85,218].

Genetic predisposition. A family history of cardiovascular disease has been associated with cardiovascular disease in patients with diabetic nephropathy [125]. In addition, a family history of type 2 diabetes has been associated with coronary heart disease [128], and in another study both a family history of type 2 diabetes and hypertension were associated with an intermediate marker of atherosclerosis, the carotid intima-media thickness [219].

Glycemic control. The role of glycemic control in cardiovascular disease has only recently started to unravel. Weak associations between glycemic control and coronary heart disease have been observed in some [220] but not all earlier studies [19,208]. The DCCT originally showed a 41% risk reduction in cardiovascular disease by intensive treatment of diabetes. This risk reduction was, however, not statistically significant in the young patients with few cardiovascular events [144]. Six years after the DCCT closeout, the intensive treatment received during the DCCT, decreased the progression of carotid intima-media thickness [221]. Twelve years after the DCCT closeout, the effect of intensive treatment was preserved, resulting in a 42% lower risk of any cardiovascular events, an observation that was significant also after adjustment for albuminuria [222]. Similarly, coronary artery calcification was measured with computed tomography eight years after the end of DCCT, and patients with prior intensive treatment had less atherosclerosis mainly due to reduced HbA_{1c} levels during the DCCT [223]. Suboptimal glycemic control was also a strong risk factor for progression of coronary artery calcification in a smaller study [224]. Recent data from the DCCT show poor glycemic control to be a risk factor for the development of hypertension, which again is a risk factor for cardiovascular disease [225]. Further evidence for the role of poor glycemic control in type 1 diabetes comes from a meta-analysis showing that improvement of glycemic control results in a 62% lower risk of macrovascular events [226]. Also recent prospective studies demonstrate a beneficial effect of good glycemic control on cardiovascular morbidity and

mortality in type 1 diabetes [209,227,228].

Hypertension. Hypertension has been demonstrated in many studies to increase the risk of cardiovascular morbidity and mortality in patients with type 1 diabetes [19,204,229,230]. Some studies have not been able to show an effect of hypertension independently of diabetic nephropathy [208], while in other studies the risk associated with hypertension has been restricted to females [216].

Dyslipidemia. Cardiovascular disease in type 1 diabetes is associated with higher triglycerides and lower HDL-cholesterol [205], as well as with changes in the composition of the lipoproteins [231]. In prospective studies, elevated total cholesterol [229] and low HDL-cholesterol [19,208,230] have been shown to predict cardiovascular disease. High triglycerides seem to increase the risk of cardiovascular disease primarily in females [216].

Obesity. A measure of abdominal obesity, the waist-to-hip ratio, has been associated with increased risk of cardiovascular disease in both males and females with type 1 diabetes [208,216]. Body mass index, a general measure of obesity, has been associated with the progression of coronary artery calcification [232].

Insulin resistance. Early studies reported that insulin resistance is associated with atherosclerosis [233], and also with the progression of atherosclerotic disease in follow-ups of 7 years [234] and 18 years of the same cohort of patients with type 1 diabetes [235]. In addition, independent relationships between an estimate of insulin resistance and both cardiovascular events [19] and coronary artery calcification have been observed [236].

Other factors. Cardiac autonomic neuropathy is a strong risk factor for cardiovascular morbidity [200,216], and reduced heart rate variability, a measure of autonomic dysfunction, has been associated with coronary artery calcification in patients with type 1 diabetes [237]. Chronic low-grade inflammation and endothelial dysfunction also increase the risk of cardiovascular morbidity and mortality [187,230,238]. In addition, smoking increases the risk of both peripheral vascular disease [230] and coronary heart disease [19,208,216].

The metabolic syndrome

History and definitions

Risk factors associated with cardiovascular disease, including impaired glucose regulation, central obesity, dyslipidemia, and hypertension, tend to cluster in the same individuals. Reaven called this syndrome the Syndrome X, a cluster of insulin resistance with dyslipidemia and hypertension [239]. Kaplan added abdominal obesity to the syndrome, and named it the Deadly Quartet [240]. Thereafter, the syndrome has also been called the insulin resistance syndrome [241], but today this syndrome is known worldwide as the metabolic syndrome.

Already in the 18th century, Morgagni described the coexistence of visceral fat accumulation with metabolic abnormalities and cardiovascular disease [242]. This matter was reawakened in 1923, when Kylin presented his hypertension-hyperglycemia-hyperuricemia syndrome [243]. It was not, however, until 1998 that the first definition of the metabolic syndrome was introduced by the World Health Organization (MS^{WHO}) [244], and the definition was further modified in 1999 with lower cut-off values for blood pressure [245]. Several sets of definitions with different main emphases have since been introduced by different organizations (Table 2). Both MS^{WHO} and the definition provided by the European Group for the study of Insulin Resistance (MS^{EGIR}) [246] highlight the importance of impaired glucose regulation. The definitions by the National Cholesterol and Education Program Adult Treatment Panel III (MS^{NCEP}) [247] and the American Heart Association and the National Heart, Lung, and Blood Institute ($MS^{AHA/NHLBI}$) [248] give all the components equal importance and define the disturbance in

Table 2. Definitions of the metabolic syndrome.

	WHO 1999	EGIR 1999	NCEP 2001	IDF 2005	AHA/NHLBI 2005
General	Diabetes, IGT, or insulin resistance + 2 other	Plasma insulin >75th percentile + 2 other	3 of the following:	Abdominal obesity + 2 other	3 of the following:
Abdominal obesity	BMI >30 kg/m^2 and/or WHR M >0.90 F >0.85	Waist circumference M ≥94 cm F ≥80 cm	Waist circumference M >102 cm F >88 cm	Waist circumference M ≥94 cm F ≥80 cm	Waist circumference M ≥102 cm F ≥88 cm
Hypertension	≥140/≥90 mmHg	≥140/≥90 mmHg or treatment	≥130/≥85 mmHg	≥130/≥85 mmHg or treatment	≥130/≥85 mmHg or treatment
HDL-cholesterol	HDL M <0.9 mmol/l, F <1.0 mmol/l and/or triglycerides ≥1.7 mmol/l	HDL <1.0 mmol/l and/or triglycerides ≥2.0 mmol/l or treatment	M <1.0 mmol/l F <1.3 mmol/l	M <1.03 mmol/l, F <1.29 mmol/l, or treatment	M <1.03 mmol/l, F <1.30 mmol/l, or treatment
Triglycerides			≥1.7 mmol/l	>1.7 mmol/l or treatment	≥1.7 mmol/l or treatment
Hyperglycemia (fP-glucose)	Diabetes, IGT, or insulin resistance	≥6.1 mmol/l or IGT, but not diabetes	≥6.1 mmol/l or diabetes	≥5.6 mmol/l or diabetes	≥5.6 mmol/l or treatment
UAER	≥20 μg/min	-	-	-	-

WHO = World Health Organization, EGIR = European Group for the study of Insulin Resistance, NCEP = National Cholesterol Education Program Adult Treatment Panel III, IDF = International Diabetes Federation, AHA/NHLBI = American Heart Association/National Heart, Lung, and Blood Institute, IGT = impaired glucose tolerance, BMI = body mass index, WHR = waist-to-hip ratio, M = males, F = females, UAER = urinary albumin excretion rate.

glucose regulation by impaired fasting glucose. The definition by the International Diabetes Federation (MS^{IDF}) [249] considers abdominal obesity as the central feature and also provides ethnicity-specific cut-off values for waist circumference. Irrespective of which definition is used, the main components of the syndrome remain the same. Notably, the MS^{WHO} is the only one to include microalbuminuria, which is a strong predictor of cardiovascular disease [217]. The earlier definitions, MS^{WHO} and MS^{EGIR}, included insulin resistance as a specific component [245,246], however, the exact measurement of insulin sensitivity is difficult, and later definitions have therefore instead included fasting plasma glucose as a measure of impaired glucose regulation. Of note is that none of the definitions for the metabolic syndrome has taken into consideration patients with type 1 diabetes.

Epidemiology

With the worldwide increase in obesity, the metabolic syndrome has become a frequently observed condition, and the many definitions provided have enabled assessment of the prevalence of the metabolic syndrome in different populations. In Finland, the metabolic syndrome is observed in 39% and 22% of middle-aged males and females, respectively, according to a modified MS^{WHO} definition [250], and the prevalence of the metabolic syndrome increases with age [16]. In young Finnish adults, the prevalence is 13% , 14%, and 10% according to MS^{NCEP}, MS^{IDF}, and MS^{EGIR}, respectively, and a 7-fold increase in the metabolic syndrome in 24-year-olds from 1986 to 2001 has emerged, driven mainly by an increase in obesity and dyslipidemia [15]. An increase in the metabolic syndrome has also been observed in middle-aged Finnish females, but not significantly in males

[251]. According to the MS^{NCEP} definition, the prevalence in adult males worldwide ranges from 10% in France and India, to 15 to 20% in Australia, Ireland, and Italy, and further to 25% in Turkey. In females, the prevalence is less than 10% in France, 20% in Australia, Ireland, and Oman, and 40% in Iran and Turkey [252]. In the United States, the overall prevalence is 22%, exceeding 40% in those aged over 60 years. The metabolic syndrome is also more common among Mexican Americans and African American females [253]. A considerable overlap exists between the different definitions, as MS^{WHO} and MS^{NCEP} identify with 86% accuracy the same individuals [254].

Cardiovascular disease and the metabolic syndrome

In a recent meta-analysis, the metabolic syndrome was shown to increase the risk of cardiovascular morbidity and mortality 1.5- and 1.7-fold, respectively [255], and this increased risk is observed in both the general population and patients with type 2 diabetes [16,256-258]. The metabolic syndrome is consequently a frequent finding in patients with cardiovascular disease, being observed in 40 to 50% of patients with manifest disease [259,260]. The metabolic syndrome increases the progression of carotid atherosclerosis [261] and worsens the prognosis of patients with cardiovascular disease [259,260]. The MS^{NCEP} compared with the MS^{IDF}, is a better predictor of future outcome of patients with established vascular disease [259,260].

Diabetes and the metabolic syndrome

The metabolic syndrome increases with more pronounced disturbances in glucose regulation, being 12% in subjects with normal glucose tolerance, 53% in subjects with either impaired fasting glucose or impaired glucose tolerance, 75% in subjects with impaired glucose tolerance, and 87% in subjects with type 2 diabetes [16,250]. The metabolic syndrome is thought to be a pre-diabetic state, associated with a 3-fold risk of developing type 2 diabetes [44,262,263]. Type 2 diabetes is also associated with a worse prognosis after a cardiovascular event [264,265]. The role of the metabolic syndrome in patients with type 1 diabetes is unknown.

Renal disease and the metabolic syndrome

More recently, attention has been drawn to the association of the metabolic syndrome with chronic renal disease. In subjects without diabetes, the metabolic syndrome has been associated with the presence [266] as well as the development of chronic renal disease [14]. In patients with type 2 diabetes, the metabolic syndrome is associated with a 4-fold risk ratio for microalbuminuria, an association mainly driven by hypertension [267]. A metabolic profile related to insulin resistance has also been associated with a reduction in renal function in patients with type 2 diabetes [268]. The association of the metabolic syndrome with renal disease is unsurprising given the strong association between cardiovascular and renal disease. Moreover, insulin resistance, dyslipidemia, and hypertension are all risk factors for renal disease and also co-occur with renal disease.

Other conditions and the metabolic syndrome

The metabolic syndrome is also associated with many other conditions. A reciprocal association exists between psychological distress and the metabolic syndrome. During a 7-year follow-up of middle-aged women, depression, tension, and anger increased the risk of the metabolic syndrome, which in turn increased the risk of developing anxiety [269]. Chronic schizophrenia is associated with a considerable increase in the prevalence of the metabolic syndrome, driven by adverse metabolic effects of antipsychotic medication, along with such life style factors as smoking, lack of exercise, and poor diet [270]. Polycystic ovary syndrome is considered to be an insulin resistant state, and the metabolic syndrome has accordingly been associated with this condition [271]. In addition, sleep apnea is associated with an increased prevalence of the metabolic syndrome, and the association is thought to be mediated via fragmentation of sleep and hypoxia, and to result in metabolic disorders via oxidative stress, inflammation, and activation of the sympathetic nervous system [272]. Further-

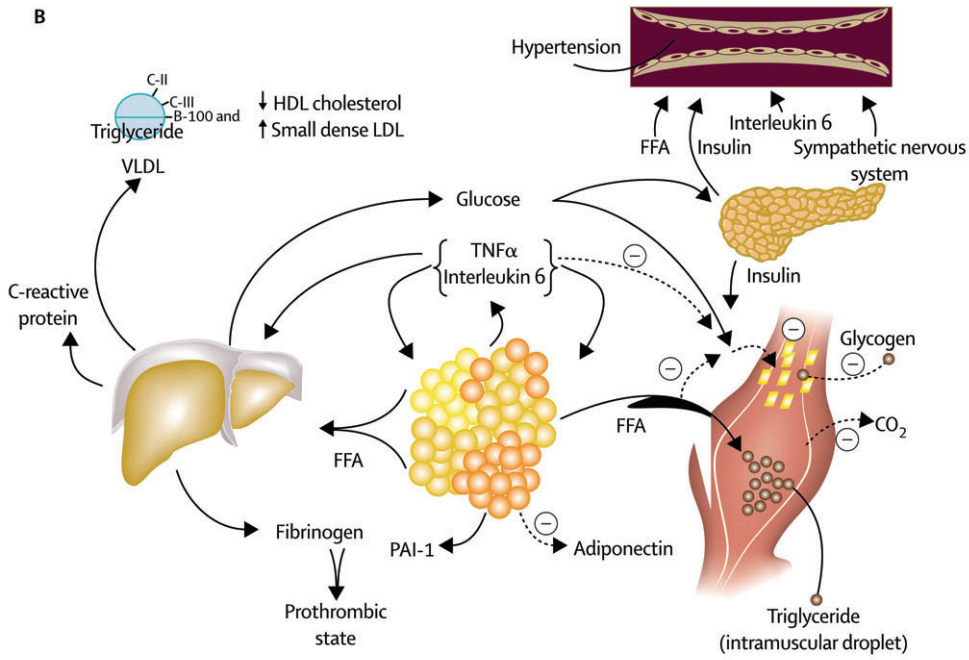


Figure 1. Pathogenesis of the metabolic syndrome and insulin resistance. Reprinted from The Lancet 365, Eckel RH, Grundy SM, and Zimmet PZ, The metabolic syndrome, pages 1415-1428, Copyright © 2005, with permission from Elsevier.

more, the metabolic syndrome is a risk factor for prostate cancer, especially in obese individuals [273], and also increases the risk of other forms of cancer, for example colon cancer [274]. The metabolic syndrome is also more common in subjects who smoke and are less physically active, observed especially in those who belong to lower social classes [275].

Pathogenesis

Insulin resistance has been proposed as the underlying factor behind the clustering of the metabolic abnormalities observed in the metabolic syndrome [239]. Figure 1 depicts the pathophysiology of the metabolic syndrome and insulin resistance [252]. An overabundance of free fatty acids, as a result of increased lipolysis in adipose tissue, especially in visceral deposits, plays a major role in the development of insulin resistance [276]. Free fatty acids reduce insulin-mediated glucose uptake in muscles and increase glucose production in the liver by impaired insulin action and enhanced gluconeogenesis. In the liver, free fatty acids also increase secretion of triglyceride-rich very low-density lipoproteins, leading to decreased HDL-cholesterol and increased density of LDL-cholesterol.

Lipoprotein lipase plays a central role in the metabolism of triglyceride-rich particles and low activity of lipoprotein lipase leads to elevated triglycerides and low HDL-cholesterol. Lipoprotein lipase activity is insulin-dependent, and is thus low in insulin resistance and also in insulin deficiency [162]. Furthermore, increased circulating glucose and also free fatty acids to some extent lead to increased insulin secretion of pancreatic β-cells, resulting in hyperinsulinemia. Hyperinsulinemia further causes sodium reabsorption in the kidneys and increased central nervous system activity, contributing to hypertension [252].

In obesity, the adipose tissue is characterized by enlarged adipocytes and increased macrophage infiltration. The enlarged adipocytes produce increased amounts of proinflammatory cytokines, such as interleukin-6, which together with the macrophage-produced tumor necrosis fac-

tor α, are involved in impaired insulin signaling. Adipocytes also produce adipokines, such as leptin and the anti-inflammatory adiponectin [277]. The increased secretion of cytokines combined with decreased adiponectin secretion lead to increased free fatty acid release. They also contribute to insulin resistance in muscles and liver and have direct harmful effects on the vasculature, eventually leading to atherosclerosis [278]. Adipocytes also secrete angiotensinogen, thereby contributing to hypertension via activation of the renin-angiotensin system. In addition, plasminogen activator inhibitor-1 production by adipose tissue is increased in obesity, contributing to a prothrombotic state [277].

In addition, neuroendocrine dysregulation of the hypothalamic-pituitary-adrenal axis may be involved in the metabolic syndrome. In males, low testosterone levels lead to muscular insulin resistance and in combination with elevated cortisol to fat accumulation in visceral deposits. In females, high levels of adrenal androgens via activation of the hypothalamic-pituitary-adrenal axis lead to insulin resistance.[279]

Components of the metabolic syndrome

Insulin resistance

Insulin resistance is defined as a reduced biological effect for a given insulin concentration [180]. There are several ways to measure insulin resistance. The euglycemic clamp technique is the golden standard [175], although time-consuming and thus used only in studies with small numbers of patients. In subjects without exogenous insulin therapy, an alternative method for measuring insulin resistance is the minimal model, which assesses the profiles of insulin and glucose during an intravenous glucose tolerance test. While these two methods assess the stimulated insulin resistance, the homeostasis assessment model estimates basal insulin resistance. The homeostasis assessment model is a mathematical model based on fasting plasma glucose and insulin concentrations, and can thus be performed in large study populations. A more simplistic approach, although not as accurate, is to measure fasting insulin [180]. Insulin resistance as an independent cardiovascular risk factor is somewhat contradictory. Not all studies have been able to demonstrate a positive association, but a meta-analysis showed hyperinsulinemia to be a risk factor for cardiovascular disease [280]. Insulin resistance is, however, strongly associated with both the individual components of the metabolic syndrome, such as triglycerides, low HDL-cholesterol, hypertension, obesity, and albuminuria [281], and the cluster of these components [282,283]. Insulin resistance adds to the value of MS^{NCEP} in the prediction of cardiovascular events, even after adjustment for traditional risk factors and type 2 diabetes [284]. Insulin resistance also predicts the development of type 2 diabetes independent of obesity [285].

Abdominal obesity

Insulin resistance is characteristic of obesity, although lean people can also be insulin resistant [286]. Obesity is associated with all of the components of the metabolic syndrome [287]. Visceral fat, in contrast to subcutaneous fat, is especially harmful, and measured by the waist-to-hip ratio, visceral fat is independently associated with an increased cardiovascular risk, after adjustment for body mass index and other cardiovascular risk factors [288]. Detection of visceral fat by magnetic resonance imaging shows waist circumference to be superior to waist-to-hip ratio and body mass index in detecting visceral fat [289,290]. Visceral fat is thought to have adverse metabolic effects due to higher turnover rate and flux of free fatty acids to the liver [252].

Dyslipidemia

In line with the proposed pathophysiology behind the metabolic syndrome, high levels of triglycerides and low levels of HDL-cholesterol are associated with insulin resistance [239]. Especially the combination of these two lipid abnormalities is associated with a number of other metabolic disturbances as well, while low HDL-cholesterol without elevated triglycerides is not associated with insulin resistance or ab-

dominal obesity [291]. In addition, insulin resistance seems to precede the development of dyslipidemia [292]. Small dense LDL-cholesterol is frequently observed in patients with the metabolic syndrome, but is often not an independent risk factor for cardiovascular disease [293].

Hypertension

The association between hypertension and insulin resistance is weaker than for the other components, although abundant data favor the view that hypertension is a true component of the metabolic syndrome. Lean hypertensive patients are insulin resistant [294], and in subjects with normal glucose regulation, fasting insulin, an indicator of insulin resistance, is associated with hypertension [295]. In addition, fasting insulin also predicts the development of hypertension [292]. Furthermore, subjects with normal blood pressure, but with a family history of hypertension, are more insulin resistant and have higher triglycerides and lower HDL-cholesterol than subjects without this family history [296,297]. Hypertensive subjects also have elevated triglycerides and lower HDL-cholesterol [298], and the cluster of atherogenic lipid abnormalities might even precede the development of hypertension [299]. Hypertensive patients with the metabolic syndrome also have higher urinary albumin excretion, despite similar blood pressure values, than those without the metabolic syndrome [300]. In patients with hypertension, the metabolic syndrome is associated with a 43% increased risk of cardiovascular events, after adjustment for traditional risk factors and diabetes [301].

Albuminuria

The MS^{WHO} is the only definition to include microalbuminuria in the metabolic syndrome [245]. Albuminuria is associated with insulin resistance in patients with hypertension, and the presence of diabetes is associated with a further reduction in insulin sensitivity [302,303]. Subjects with a cluster of type 2 diabetes, hypertension, and microalbuminuria have a dyslipidemia typical of the metabolic syndrome [303]. Albuminuria is also associated with an increased waist-to-hip ratio in healthy subjects receiving no medication [304].

Other metabolic abnormalities

The metabolic syndrome is also closely associated with metabolic abnormalities other than those included in the definitions of the syndrome. The metabolic syndrome is associated with elevated uric acid [305], as well as with decreased levels of adipokines and increased levels of inflammatory cytokines, and the prothrombotic plasminogen activator inhibitor-1 [306]. Nonalcoholic fatty liver is closely associated with the components of the metabolic syndrome [307]. Of the markers of inflammation, C-reactive protein is established as a cardiovascular risk factor. Elevated C-reactive protein is associated with obesity [308], the development of hypertension [309], and an increased risk of the metabolic syndrome [308]. The combination of C-reactive protein and the metabolic syndrome adds to the risk of developing cardiovascular disease beyond the risk associated to the metabolic syndrome alone. This suggests that C-reactive protein could work as an additional component of the metabolic syndrome [310]. Moreover, a low birth weight combined with a catch-up in body weight is associated with the occurrence of the metabolic syndrome later in life [311]. This could indicate that fetal and childhood growth plays a role in the development of metabolic disturbances leading to the metabolic syndrome, cardiovascular disease, and diabetes, a theory initiated by Barker [312].

3 AIMS OF THE STUDY

The aims of this study were as follows:

I To investigate the association between parental history of hypertension, cardiovascular disease, and diabetes, and diabetic nephropathy in offspring, in a large cohort of patients with type 1 diabetes, and to assess whether clustering of such traits in families increases the likelihood of diabetic nephropathy. Another aim was to investigate whether parents of patients with diabetic nephropathy have an increased total or cardiovascular mortality.

II To evaluate the effect of parental history of type 2 diabetes on offspring with type 1 diabetes, with regard to their metabolic profile and the presence of the metabolic syndrome and diabetic late complications.

III To assess the prevalence of the metabolic syndrome in Finnish patients with type 1 diabetes and to evaluate whether it is associated with diabetic nephropathy or poor glycemic control.

IV To assess the predictive value of different definitions of the metabolic syndrome for cardiovascular events, cardiovascular and diabetes-related mortality, and progression of diabetic nephropathy in patients with type 1 diabetes.

4 SUBJECTS AND STUDY DESIGNS

The FinnDiane Study – general aspects

All patients are part of the nationwide FinnDiane Study that was launched on November 21, 1997, at the Helsinki University Central Hospital, Department of Medicine, Division of Nephrology. The aims of the study are to collect a large cohort of adult patients with type 1 diabetes (25%) from all over Finland, and to find genetic, clinical, and environmental risk factors for micro- and macrovascular complications in type 1 diabetes. The study includes 77 centers participating in the collection of patients, including all 5 University Hospitals, all 16 Central Hospitals, 26 regional hospitals, and 30 primary health care centers (see Appendix). The local ethics committees have approved the study protocol, and the study has been carried out in accordance with the Declaration of Helsinki [313]. Written informed consent was obtained from each patient.

The FinnDiane Study consists of three phases that being conducted in parallel. *Phase I* includes a visit to collect baseline data of patients with type 1 diabetes. *Phase I* is ongoing, and by November 2008, a total of 4,805 patients with type 1 diabetes had participated, that is approximately 12% of all 40,000 patients with type 1 diabetes in Finland. The patients are from all over Finland, as shown in Figure 2.

In *phase II* of the FinnDiane Study, parents and siblings of the patients with type 1 diabetes are investigated. By November 2008, a total of 1,652 parents and 799 siblings had participated. Two different approaches are used. The primary approach includes a visit to one of the study centers and collection of clinical and laboratory data (n = 965). The secondary approach includes mailing out a questionnaire and test tubes for blood samples that are then drawn at the participant's local laboratory and sent to the FinnDiane Study by mail (n = 1,450). Finally, in some cases, house calls have been made to collect both clinical and laboratory data (n = 36).

Phase III of the FinnDiane Study consists of collection of follow-up data of the patients with type 1 diabetes who have participated in *phase I* of the study. *Phase III* was initiated in 2004, is still ongoing, and the goal is to re-study all patients who participated in *phase I*. By November 2008, altogether 1,268 patients had been re-studied. Alternative approaches to collect follow-up data include visiting hospital archives to review the medical files of patients or ordering specific medical files (n = 3,108).

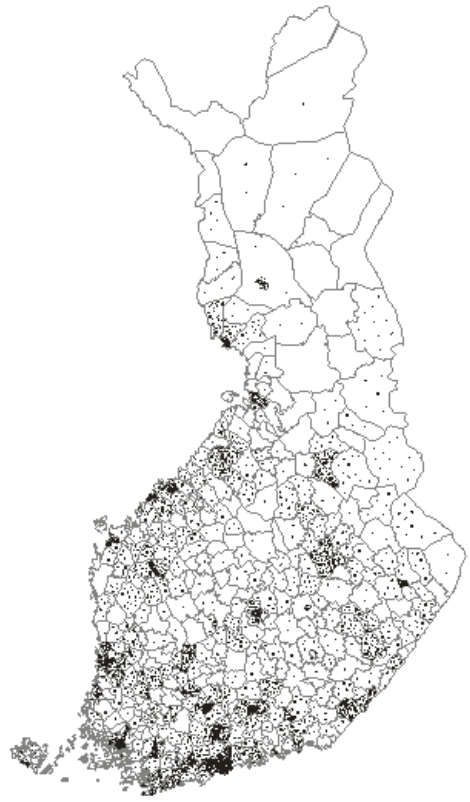


Figure 2. Map of Finland with each dot indicating the home address of one FinnDiane Study subject. The distribution is similar to the distribution of people in Finland in general, with most people living in the southern parts of the country.

For patients who have died, death certificates are ordered to retrieve information on time and cause of death (see more detailed information in the Methods section).

All clinical data, laboratory data, genetic data, and data from questionnaires are entered into the web browser-based platform BC/GENE version 3.0 (Biocomputing Platforms Ltd., Espoo, Finland). When the different studies were performed, the complete data set available from the database at the time of each study was used, and the selection criteria for each study are provided below.

Study I

The design for Study I is cross-sectional. By May 2005, the study included 2,355 patients with type 1 diabetes for whom the diabetic renal status was classifiable and information on either parent was available. Of the patients, 51% were male, mean age was 41.1 ± 10.9 years (mean ± standard deviation), and duration of diabetes was 28.2 ± 9.2 years. Information was available for 2,353 mothers and 2,323 fathers, a total of 4,676 parents. More detailed clinical characteristics of the patients, grouped by the presence or absence of diabetic nephropathy, are shown in Table 3.

Table 3. Clinical characteristics of patients with and without diabetic nephropathy in Study 1 (n = 2,355)

	Diabetic nephropathy n = 780	No diabetic nephropathy n = 1,575	P value
Males (%)	59	48	<0.001
Age (years)	42.1 ± 9.4	40.6 ± 11.6	0.002
Age at diabetes onset (years)	11.6 ± 7.1	13.6 ± 8.3	<0.001
Duration of diabetes (years)	30.4 ± 8.0	27.0 ± 9.6	<0.001
Body mass index (kg/m^2)	25.2 ± 3.9	25.1 ± 3.3	0.594
Waist circumference (cm)	89 ± 12	85 ± 11	<0.001
Total cholesterol (mmol/l)	5.46 ± 1.11	4.94 ± 0.87	<0.001
LDL-cholesterol (mmol/l)	3.44 ± 0.94	3.01 ± 0.81	<0.001
HDL-cholesterol (mmol/l)	1.26 ± 0.39	1.45 ± 0.47	<0.001
Triglycerides (mmol/l)	1.41 (1.02-2.03)	0.93 (0.70-1.26)	<0.001
Lipid-lowering medication (%)	23	9.0	<0.001
Treatment with acetylsalicylic acid (%)	32	9.5	<0.001
HbA_{1c} (%)	8.9 ± 1.5	8.3 ± 1.3	<0.001
eGDR (mg/kg/min)	4.0 (3.1-5.0)	6.4 (4.6-8.5)	<0.001
Insulin dose (IU/kg)	0.67 (0.54-0.80)	0.66 (0.54-0.80)	0.780
eGFR (ml/min/1.73m^2)	60 ± 35	101 ± 29	<0.001
UAER (mg/24h)	499 (171-1274)	11 (6-29)	<0.001
Systolic blood pressure (mmHg)	147 ± 21	133 ± 16	<0.001
Diastolic blood pressure (mmHg)	84 ± 11	79 ± 9	<0.001
Antihypertensive medication (%)	95	34	<0.001
ACE-inhibitors/AT2-blockers (%)	57/9.6	24/3.9	<0.001
Coronary heart disease (%)	15	4.1	<0.001
Myocardial infarction (%)	8.6	1.9	<0.001
Stroke (%)	7.2	1.1	<0.001
Amputations (%)	11	1.1	<0.001
Smoking (%)	25	22	0.144
Age of mothers (years)	66.6 ± 10.0	64.6 ± 11.6	<0.001
Age of fathers (years)	66.0 ± 8.7	64.2 ± 10.4	0.005
Age at death of mothers (years)	69.3 ± 13.7	69.4 ± 12.9	0.958
Age at death of fathers (years)	63.8 ± 13.2	64.1 ± 13.7	0.753

Data are means ± standard deviations, medians (interquartile ranges), or percentages. eGDR = estimated glucose disposal rate, eGFR = estimated glomerular filtration rate, UAER = urinary albumin excretion rate.

Study II

The design for Study II is cross-sectional. The study includes 1,860 patients with type 1 diabetes. The selection of patients for the study is shown in Figure 3. In March 2006, complete information on the metabolic syndrome, renal status, and parental medical history was available for 3,037 patients. A clear age difference was present between patients with a positive parental history of type 2 diabetes, compared with those with a negative parental history (43.9 ± 10.2 vs. 36.0 ± 11.5 years, $P<0.001$), and therefore of the 2,417 patients with a negative parental history of type 2 diabetes, a total of 1,240 age-matched patients were randomly selected as controls. The matching for age was first done by dividing those with a positive parental history of type 2 diabetes into octiles regarding age. Those with a negative parental history of diabetes were then ordered by a random number from zero to one. Thereafter the controls were chosen, within the same age-limits, in numerical order in 1:2 ratio from each age group. More detailed clinical characteristics of the patients, grouped by their family history of type 2 diabetes, are shown in Table 8 (Section 6).

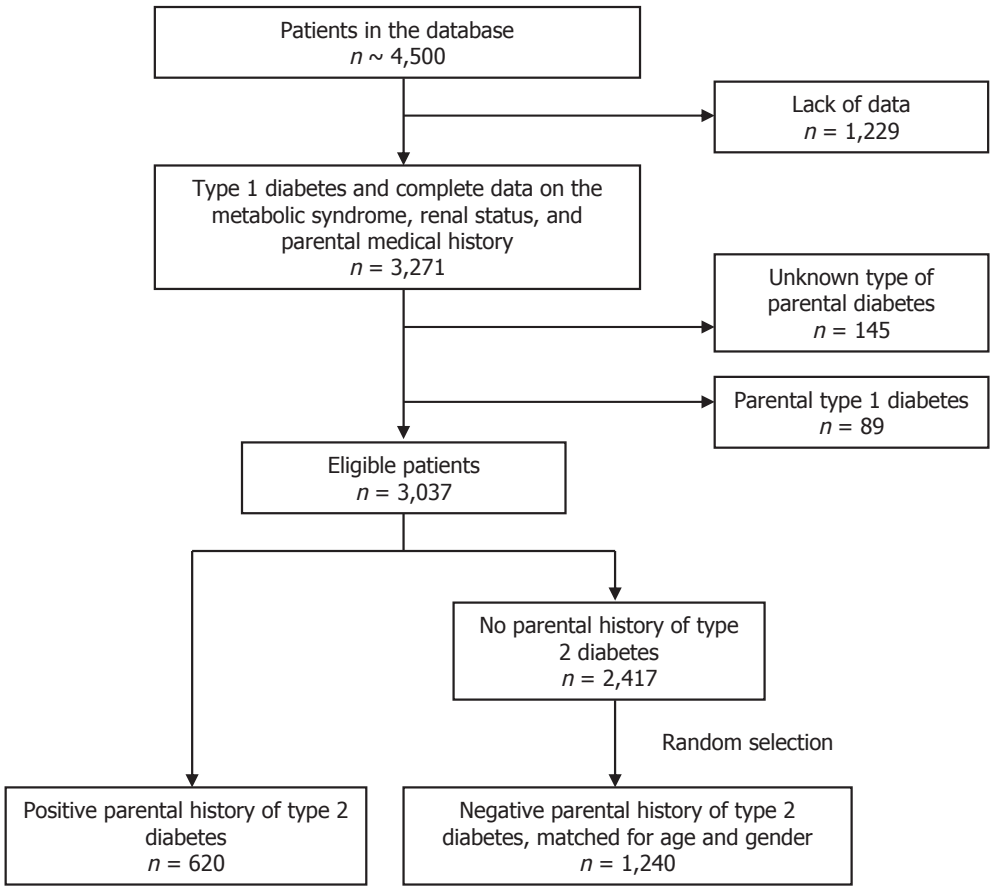


Figure 3. Selection of patients for Study II.

Study III

The design for Study III is cross-sectional. The study includes 2,415 patients with type 1 diabetes for whom complete lipid profiles and clinical data on the components of the metabolic syndrome were available by April 2004. Of the patients, 51% were male, mean age was 37.1 ± 11.6 years, and duration of diabetes was 21.9 ± 11.7 years. More detailed clinical characteristics of the patients, grouped by the presence or absence of the metabolic syndrome, are shown in Table 4.

Study IV

Study IV is a prospective study. The study includes 3,783 patients with type 1 diabetes in whom, at baseline, complete data on lipid profiles and clinical data on all of the components of the metabolic syndrome were available by March 2008. Of the patients, 52% were male, mean age was 37.5 ± 11.8 years, and duration of diabetes was 22.7 ± 12.2 years. More detailed clinical characteristics of the patients, grouped by the presence or absence of the metabolic syndrome, are shown in Table 5.

Table 4. Clinical characteristics of patients with and without the metabolic syndrome in Study III (n = 2,415)

	Metabolic syndrome n = 944	**No metabolic syndrome n = 1,471**	**P value**
Males (%)	50	52	0.448
Age (years)	38.7 ± 11.6	36.2 ± 11.5	<0.001
Age at diabetes onset (years)	14.5 ± 8.2	15.7 ± 8.7	0.001
Duration of diabetes (years)	24.1 ± 11.1	20.5 ± 11.8	<0.001
Body mass index (kg/m^2)	26.6 ± 4.0	24.0 ± 2.7	<0.001
Waist-to-hip ratio (cm)	0.90 ± 0.09	0.85 ± 0.08	<0.001
Total cholesterol (mmol/l)	5.21 ± 1.01	4.82 ± 0.87	<0.001
LDL-cholesterol (mmol/l)	3.34 ± 0.90	2.93 ± 0.81	<0.001
HDL-cholesterol (mmol/l)	1.10 ± 0.30	1.43 ± 0.35	<0.001
Triglycerides (mmol/l)	1.53 (1.03-2.11)	0.92 (0.74-1.18)	<0.001
Lipid-lowering medication (%)	16	6.1	<0.001
Treatment with acetylsalicylic acid (%)	17	7.2	<0.001
HbA_{1c} (%)	8.8 ± 1.6	8.3 ± 1.4	<0.001
eGDR (mg/kg/min)	4.5 (3.2-6.1)	7.2 (4.9-8.8)	<0.001
Insulin dose (IU/kg)	0.71 (0.58-0.87)	0.67 (0.55-0.82)	<0.001
Creatinine (μmol/l)	92 (79-117)	84 (76-95)	<0.001
eGFR (ml/min/1.73m^2)	89 (65-105)	94 (79-108)	<0.001
Systolic blood pressure (mmHg)	140 ± 19	130 ± 18	<0.001
Diastolic blood pressure (mmHg)	83 ± 10	78 ± 10	<0.001
Antihypertensive medication (%)	61	30	<0.001
ACE-inhibitors/AT2-blockers (%)	39/7.1	21/3.3	<0.001
Coronary heart disease (%)	8.7	3.4	<0.001
Myocardial infarction (%)	5.1	1.5	<0.001
Stroke (%)	3.1	1.5	0.009
Diabetic nephropathy (%)	37	14	<0.001
Retinal laser treatment (%)	53	26	<0.001
Smoking (%)	26	22	0.037

Data are means ± standard deviations, medians (interquartile ranges), or percentages. eGDR = estimated glucose disposal rate, eGFR = estimated glomerular filtration rate.

Table 5. Baseline clinical characteristics of the patients by the different definitions of the metabolic syndrome in Study IV (n = 3,783)

	MS^{WHO+} n = 1,650	MS^{WHO-} n = 2,133	P value	MS^{NCEP+} n = 1,315	MS^{NCEP-} n = 2,468	P value	MS^{IDF+} n = 1,311	MS^{IDF-} n = 2,347	P value
Males (%)	63	43	<0.001	52	51	0.549	44	56	<0.001
Age (years)	40.5 ± 11.3	35.1 ± 11.7	<0.001	39.0 ± 11.7	36.7 ± 11.9	<0.001	40.6 ± 11.6	35.7 ± 11.6	<0.001
Age at diabetes onset (years)	13.9 ± 8.2	15.5 ± 8.6	<0.001	14.2 ± 8.2	15.1 ± 8.6	0.004	15.1 ± 8.4	14.6 ± 8.5	0.143
Duration of diabetes (years)	26.7 ± 11.3	19.6 ± 11.9	<0.001	24.8 ± 11.6	21.6 ± 12.3	<0.001	25.6 ± 11.7	21.1 ±12.2	<0.001
Body mass index (kg/m^2)	26.1 ± 3.9	24.1 ± 2.9	<0.001	26.7 ± 4.1	24.1 ± 2.8	<0.001	27.8 ± 3.4	23.4 ± 2.5	<0.001
Waist circumference (cm)	91 (84-98)	81 (75-87)	<0.001	92 (83-101)	82 (76-88)	<0.001	95 (86-101)	79 (74-87)	<0.001
Total cholesterol (mmol/l)	5.24 ± 1.07	4.73 ± 0.96	<0.001	5.21 ± 1.11	4.81 ± 0.98	<0.001	5.19 ± 1.01	4.82 ± 1.04	<0.001
LDL-cholesterol (mmol/l)	3.29 ± 0.93	2.88 ± 0.92	<0.001	3.30 ± 0.94	2.93 ± 0.92	<0.001	3.25 ± 0.90	2.94 ± 0.95	<0.001
HDL-cholesterol (mmol/l)	1.21 ± 0.39	1.41 ± 0.36	<0.001	1.09 ± 0.33	1.45 ± 0.36	<0.001	1.25 ± 0.37	1.36 ± 0.39	<0.001
Triglycerides (mmol/l)	1.37 (0.96-2.00)	0.90 (0.70-1.17)	<0.001	1.62 (1.04-2.21)	0.91 (0.71-1.18)	<0.001	1.23 (0.88-1.79)	0.96 (0.73-1.33)	<0.001
Lipid-lowering medication (%)	19	5.2	<0.001	17	7.6	<0.001	19	6.8	<0.001
Treatment with acetylsalicylic acid (%)	21	6.4	<0.001	19	9.1	<0.001	19	9.3	<0.001
HbA_{1c} (%)	8.7 ± 1.5	8.2 ± 1.4	<0.001	8.8 ± 1.6	8.3 ± 1.4	<0.001	8.7 ± 1.4	8.4 ± 1.5	<0.001
eGDR (mg/kg/min)	4.2 (3.2-5.3)	8.1 (6.2-9.2)	<0.001	4.6 (3.3-6.4)	7.2 (5.0-8.9)	<0.001	4.6 (3.3-6.5)	7.2 (5.0-8.9)	<0.001
Insulin dose (IU/kg)	0.68 (0.55-0.83)	0.68 (0.54-0.84)	0.431	0.71 (0.56-0.88)	0.67 (0.54-0.83)	<0.001	0.68 (0.55-0.82)	0.69 (0.55-0.87)	0.292
Systolic blood pressure (mmHg)	144 ± 19	126 ± 14	<0.001	142 ± 18	130 ± 17	<0.001	139 ± 19	131 ± 18	<0.001
Diastolic blood pressure (mmHg)	83 ± 10	76 ± 8	<0.001	83 ± 10	77 ± 9	<0.001	82 ± 10	78 ± 10	<0.001
Antihypertensive medication (%)	66	18	<0.001	54	31	<0.001	55	31	<0.001
ACE-inhibitors/AT2-blockers (%)	43/9.0	12/2.0	<0.001	34/7.4	21/3.8	<0.001	35/9.0	20/2.8	<0.001
Cardiovascular events (%)	16	3	<0.001	14	6	<0.001	14	6	<0.001
Myocardial infarction (%)	6	1	<0.001	5	2	<0.001	5	2	<0.001
Stroke (%)	4	1	<0.001	4	2	<0.001	4	2	<0.001
Diabetic nephropathy (%)	43	4	<0.001	36	13	<0.001	29	16	<0.001
Retinal laser treatment (%)	57	17	<0.001	49	26	<0.001	45	28	<0.001
Smoking (%)	26	22	0.005	26	23	0.061	22	26	0.004

Data are means ± standard deviations, medians (interquartile ranges), or percentages. eGDR = estimated glucose disposal rate, MS^{WHO} = metabolic syndrome according to World Health Organization, MS^{NCEP} = National Cholesterol Education Program Adult Treatment Panel III, MS^{IDF} = International Diabetes Federation.

5 METHODS

The FinnDiane Study protocol

At the study centers, all adult patients with type 1 diabetes were asked to participate, and the response rate was 78% [314]. Data were collected during a regular visit to the patient's attending physician, and included a thorough medical history, current medication of the patients, and measurement of weight, height, waist and hip circumferences, and blood pressure. In addition, blood samples were drawn, and a 24-hour urine collection performed. Patients answered a questionnaire about their medical history, history of smoking, alcohol consumption, education, employment, and medical history of their siblings and parents.

Definition of type 1 diabetes
Type 1 diabetes was defined as onset of diabetes before 35 years of age and insulin treatment initiated within one year of diagnosis of diabetes.

Anthropometric measurements
Weight was measured using a standardized scale and registered to the closest 0.1 kg. Height was registered to the closest 1 cm. Body mass index was calculated as weight divided by height squared (kg/m^2). Waist circumference was measured midway between the lowest rib and the iliac crest, and hip circumferences at the widest part of the gluteal region. Waist-to-hip ratio was calculated as waist divided by hip circumference.

Assessment of blood pressure
Blood pressure was measured twice in the sitting position after an initial 10-minutes rest, and the mean values for systolic and diastolic blood pressure were calculated. The blood pressure measurements were performed with a mercury sphygmomanometer, and Korotkoff sounds I and V were registered as systolic and diastolic blood pressure, respectively. Due to regulations regarding the use of mercury sphygmomanometers in the health care service [315] (European Council Directive 93/42/EEC), automated standardized blood pressure devices have also been approved as an alternative method for measurement of blood pressure. Antihypertensive medication was defined as the current use of at least one antihypertensive drug, either angiotensin-converting enzyme inhibitor, angiotensin receptor antagonist, calcium channel blocker, β-blocker, diuretic, or other antihypertensive agents (mainly prazosin or moxonidine).

Definition of diabetic nephropathy and assessment of renal function
Renal status was defined based on the urinary albumin excretion rate in at least two of the three overnight or 24-hour urine collections. Normal urinary albumin excretion rate was defined as urinary albumin <20 μg/min or <30 mg/24h, microalbuminuria ≥20<200 μg/min or ≥30<300 mg/24h, or macroalbuminuria ≥200 μg/min or ≥300 mg/24h. Patients on dialysis or with a renal transplant were classified to having end-stage renal disease. In some patients, renal status could not be assessed due to recent onset of diabetes, too few urine collections, or signs of nondiabetic renal disease. These subjects were excluded from Studies I and II, and from part of the analyses in Studies II and IV. Diabetic nephropathy was defined as macroalbuminuria or end-stage renal disease. In Study I, patients with a normal urinary albumin excretion rate were required to have diabetes duration >15 years to ensure normal renal status.

In Studies I and III, renal function was estimated by the Cockcroft-Gault formula for creatinine clearance, adjusted for body surface area [71]. An estimated glomerular filtration rate above 90 ml/min/1.73m^2 was considered normal, 60 to 90 ml/min/1.73m^2 was considered mild renal impairment, and below 60 ml/min/1.73m^2 was considered moderate to severe renal impairment, according to American National Kidney

Foundation Kidney Disease Outcome Quality Initiative guidelines [75].

Definition of diabetic retinopathy
Retinal laser treatment was used as a marker of proliferative retinopathy. Signs of any retinal changes due to diabetes were also registered, but were not used as a variable in this study.

Definition of cardiovascular disease
Coronary heart disease was defined as diagnosed myocardial infarction, coronary revascularization, or pharmacological treatment with long-acting nitroglycerin. A myocardial infarction was defined as a clinically verified event. Stroke was defined as cerebral infarction or intracerebral hemorrhage. Cardiovascular events included diagnosed myocardial infarction, coronary revascularization, or stroke. Amputations were defined as amputation of any part of the lower limbs. The cause for amputations was not registered. Treatment with lipid-lowering medication as well as with acetylsalicylic acid was also registered.

Definition of the metabolic syndrome
The metabolic syndrome was first introduced as a concept in type 1 diabetes in Study III and assessed according to the MS^{NCEP} definition [247]. In Study II, both MS^{NCEP} and MS^{IDF} [249] definitions were used, and in Study IV, the MS^{NCEP}, MS^{IDF}, and MS^{WHO} [245] definitions were used for the diagnosis of the metabolic syndrome (Table 2). All patients with type 1 diabetes were considered to fulfill the criteria for hyperglycemia. A metabolic score (1-5) was also calculated based on the number of criteria each patient fulfilled for the MS^{NCEP} definition.

Assessment of glycemic control and insulin sensitivity
Glycemic control was assessed based on one HbA_{1c} measurement and classified as good (HbA_{1c} <7.5%), intermediate (7.5-9.0%), or poor (>9.0%). As a measure of insulin sensitivity, an equation for the estimated glucose disposal rate was applied [179], modified for use of HbA_{1c} instead of HbA_1.

Estimated glucose disposal rate =

$24.4 - 12.97*WHR - 3.39*AHT - 0.60*HbA_{1c}$

WHR stands for waist-to-hip ratio and AHT for antihypertensive treatment and/or blood pressure ≥140/90 mmHg (yes = 1, no = 0).

As another marker of insulin sensitivity, the total daily insulin dose per body weight (IU/kg) was used.

Definition of smoking
Smoking was defined as current smoking of at least one cigarette per day for at least one year.

Information on parents
Parental information was obtained from the patients with type 1 diabetes by a standardized questionnaire. Questions about mothers and fathers were asked separately, and included information on birth year, medical history of diabetes, antihypertensive medication, myocardial infarction, and stroke. Parental cardiovascular disease was defined as a history of myocardial infarction or stroke. If the parent had diabetes, age at onset and mode of treatment was registered (diet, oral hypoglycemic agents, or insulin), and based on this information the parental diabetes was classified as type 1 (age at onset <35 years and insulin treatment), type 2 (age at onset >50 years, or if age at onset was not registered, treatment with oral hypoglycemic agents or diet), or nonclassifiable (incomplete data on age at onset and/or treatment). If the parent had died, the cause and time of death was registered. Parental cardiovascular mortality was defined as death from myocardial infarction, heart failure, ruptured aortic aneurysm, or a cerebrovascular event. In Study II, of the 620 patients with a parental history of type 2 diabetes, 327 (53%) had an afflicted mother, 248 (40%) an afflicted father, and 45 (7%) had both parents afflicted.

Those with both parents with diabetes were excluded from the statistical subanalyses regarding maternal and paternal type 2 diabetes.

Parental risk score

In Study I, to assess the association of different combinations of a parental history of hypertension, cardiovascular disease, and diabetes (type 1 and type 2) with diabetic nephropathy in offspring, a parental risk score was used. Each parent was given one point for each positive history of hypertension, cardiovascular disease, and/or diabetes. If the parent had no history of these traits, the parental risk score was zero, and if the parent was positive for all three the score was three. The maximum parental score was thus six and the minimum zero. Combinations of hypertension and cardiovascular disease or diabetes were also calculated, with a maximum possible score of four. As expected, only a few patients had high scores and these scores were therefore pooled.

Validation of parental data

A total of 1,370 (29%) of the 4,676 parents in Study I participated in the FinnDiane Study. They answered a standardized questionnaire regarding their medical history. In these cases, the information given by the patient with type 1 diabetes could be directly validated. Data were validated for 625 fathers and 745 mothers of 789 patients with type 1 diabetes. Mean time difference from when the data were given by the patient with type 1 diabetes to when the parent personally attended the study was 3.1 ± 2.3 (mean ± standard deviation) years for mothers and 2.9 ± 2.5 years for fathers. In some cases, the parents had been diagnosed with hypertension, cardiovascular disease, or diabetes during this period, and the data were corrected accordingly. The overall sensitivity of the parental data was 83% and the specificity 98%. Regarding maternal/paternal data, the sensitivity for hypertension was 84/82%, myocardial infarction 75/91%, stroke 63/42%, and diabetes 91/87%.

Collection of follow-up data

Two different complementary approaches were used to collect follow-up data on the patients. First, the medical files were reviewed and any changes in renal status or occurrence of cardiovascular events was verified. Second, patients were re-examined at their local medical center according to the same protocol as at the baseline visit.

Cardiovascular events and progression of renal disease

Data collection on morbidity is ongoing, and in Study IV, data on cardiovascular events were available for 2,474 (65%), and on progression of renal disease for 2,594 (69%) patients. Data were retrieved from follow-up visits, medical files, or death certificates. A new myocardial infarction was defined as a clinically verified event during follow-up (n = 161). Stroke was defined as cerebral infarction or intracerebral hemorrhage (n = 80). Cardiovascular events included diagnosed myocardial infarction, coronary revascularization, or stroke (n = 263). Progression of renal disease was defined as a change in category from normal urinary albumin excretion to microalbuminuria (n = 118), from microalbuminuria to macroalbuminuria (n = 54), or from macroalbuminuria to end-stage renal disease (n = 130).

Mortality

On March 30, 2007, data on mortality were obtained from Statistics Finland, which maintains the national archive of death certificates. Information was obtained on which patients had died, and for those who had died, copies of the original death certificates were received. The death certificates included information on time of death, cause of death (immediate, contributing, and underlying), where the patient died (home/hospital), type of death (illness, accident, suicide, or unknown), a short report on the events prior to death, and whether the report was based on autopsy or clinical evaluation. Of the 3,783 patients in Study IV, 285 (7.5%) had died. All death certificates were re-evaluated to standardize the classification, and

coded according to the immediate and underlying causes of death. The coding included eight different categories: 1) cardiovascular disease, 2) cerebrovascular disease, 3) cancer, 4) infections, 5) diabetes, 6) accidents, 7) suicide, and 8) unknown or other causes of death. Death from any cardiovascular cause was defined as a cardiovascular (ICD 10 I21-25) or cerebrovascular (ICD10 I60-64) cause as the underlying or immediate cause of death. A diabetes-related cause was defined as diabetes (ICD10 E10) as the underlying or immediate cause of death. For analyses of mortality in Study IV, a combined end-point of cardiovascular and diabetes-related mortality was used.

Assays

Blood samples were drawn and analyzed for lipids and lipoproteins, HbA_{1c}, and creatinine, as well as for genetic analyses. A 24-hour urine collection was performed to determine the urinary albumin excretion rate. The classification of renal disease was based on local measurements of urinary albumin excretion rate in two of the three overnight or 24-hour urine collections (see classification in the beginning of Section 5).

Lipids and lipoproteins
Serum lipids and lipoproteins were measured at the research laboratory of Professor Marja-Riitta Taskinen, Department of Medicine, Division of Cardiology, Helsinki University Central Hospital, Helsinki, Finland. Serum total cholesterol concentrations were determined by enzymatic colorimetric assays (ABX Diagnostics, HORIBA ABX, Montpellier, France) until January 2006, and thereafter by enzymatic determination using a Konelab 60i analyzer (Thermo Fisher Scientific Inc., Waltham, MA, USA). Serum LDL-cholesterol was calculated using the Friedewald formula [316]:

LDL-cholesterol =

Total cholesterol – HDL-cholesterol – Triglycerides/2.2

Serum HDL-cholesterol concentrations were measured with a enzymatic colorimetric test using a HTS 7000 plus Bio Assay Reader (Perkin Elmer Inc., Waltham, MA, USA). Serum triglyceride concentrations were determined by enzymatic methods (ABX Diagnostics, HORIBA ABX, Montpellier, France) until January 2006, and thereafter by enzymatic determination using a Konelab 60i analyzer (Thermo Fisher Scientific Inc., Waltham, MA, USA).

HbA_{1c}
HbA_{1c} was determined by standardized assays at each center. In 75% of the local laboratories, the normal nondiabetic range for HbA_{1c} was 4.0-6.0%. In all centers, the upper normal limit was below 7.0%.

Creatinine
Serum creatinine was determined at a central laboratory by a kinetic Jaffe reaction using a Hitachi 911 E analyzer (Boehringer Mannheim, Mannheim, Germany), with normal reference for males of <115 μmol/l and for females <100 μmol/l, until January 2002, and thereafter by a photometric, enzymatic method using a Hitachi 917 or Modular analyzer (Boehringer Mannheim/Roche Diagnostics, Basel, Switzerland), with a normal reference for males of 50-95 μmol/l and for females 40-90 μmol/l. The correlation coefficient between the two methods was 0.988.

Urinary albumin excretion rate
Urinary albumin was determined at a central laboratory by radioimmunoassay using a LKB Wallac RiaGamma counter (Pharmacia, Uppsala, Sweden) until November 2002, and thereafter by an immunoturbidimetric method using a Hitachi 911 analyzer (Roche Diagnostics, Hoffman-La Roche, Basel, Switzerland).

HLA genotyping
DNA was extracted from whole blood according to standard protocols. In Study II, HLA genotyping was performed in a random set of 1,136 patients, including 63% of those with a positive and 60% of those with a negative pa-

rental history of type 2 diabetes. The HLA genotyping was performed in collaboration with the research team of Professor Jorma Ilonen, Immunogenetics Laboratory, University of Turku, Turku, Finland. HLA DQA1-DQB1 genotypes and DRB1*04 subtypes were identified using PCR-based lanthanide-labeled oligonucleotide hybridization and time-resolved fluorometry detection. In case the differentiation was insufficient, fluorescence-based automated DNA sequencing according to the manufacturer's instructions (MegaBace 1000, Amersham Biosciences, CA, USA) was performed.

HLA genotypes were divided into five risk categories based on their risk association with type 1 diabetes, and the observed genotype frequencies in 622 diabetic children and 622 affected family-based artificial controls in a Finnish population [24,317]. Genotypes positive for both DR3 and DR4 haplotypes [(DR3)-DQA1*05-DQB1*02/DRB1*0401/2/4/5-DQA1*03-DQB1*0302] were defined as having the highest risk.

Moderate risk genotypes included those homozygous for either DR3 or DR4 risk haplotypes, as well as genotypes composed of DR4 risk haplotypes and neutral haplotypes, or the combination of DR3 and DR9 haplotypes (DR3)-DQA1*05-DQB1*02/(DR9)-DQA1*03-DQB1*0303.

Other combinations of DR3 risk haplotype and a neutral one were defined as having a slightly increased risk. The particular combinations of weakly protective (DR13)-DQB1*0603 with strong DR4 risk haplotypes (DRB1*0401/2/5)-DQA1*03-DQB1*0302 were also included in this category based on observed frequencies.

Other genotypes with a combination of risk-associated and protective haplotypes [(DR15)-DQB1*0602,(DR7)-DQA1*0201-DQB1*0303, (DR14)-DQB1*0503, (DR11/12/13)-DQA1*05-DQB1*0301, (DR13)-DQB1*0603, DRB1*0403-DQA1*03-DQB1*0302] were defined as low-risk genotypes, and those with protective genotypes associated with neutral haplotypes or genotypes combining two protective haplotypes were classified as protective.

Replication in the DCCT (Study II)

In Study II, the publicly available database of the DCCT was used to replicate our findings. The database is available at http://www.gcrc.umn.edu/gcrc/downloads/dcct.html. The same criteria as for Study II were used for selection of patients from the database, that is adult patients with type 1 diabetes with an onset of diabetes before 35 years of age (n = 1,197). In the DCCT, a family history of type 2 diabetes was defined as a first-degree relative with type 2 diabetes [62], and 119 patients (10%) had a positive family history.

Statistical methods

The statistical significance of a difference in categorical variables between groups was tested with χ^2-test. To assess the trend in proportions over categories χ^2-test for trend analysis was used [318] (Study I). In 2x2 tables, a Mantel-Haenszel analysis was performed to adjust for age by dividing age into quartiles (Study I). Continuous variables with a normal distribution were analyzed with a t-test if two groups or ANOVA if more than two groups were compared (results are presented as means with standard deviations). Nonnormally distributed variables were analyzed with Mann-Whitney U-test if two groups and with Kruskal-Wallis H-test if more than two groups were compared (presented as medians with interquartile ranges). A P value <0.05 was considered statistically significant.

Study I

Logistic regression analyses were used to assess the association of diabetic nephropathy with different familial factors and risk scores. The models were adjusted for sex, duration of diabetes, and HbA_{1c}. Results are presented as odds ratios with 95% confidence intervals. Mortality was evaluated with Kaplan-Meier survival analy-

sis and statistical significance of differences was determined with Log rank test. In the analyses for cardiovascular mortality, only cases with known cause of death were included. All analyses were performed using SPSS 12.0.1 statistical software (SPSS Inc., Chicago, IL, USA).

Study II

Logistic regression analyses were used to test which variables were independently associated with a parental history of type 2 diabetes. Variables were included in multivariate models if $P < 0.05$ in the univariate analyses. Results are presented as odds ratios with 95% confidence interval. All analyses were performed using SPSS 15.0 statistical software (SPSS Inc., Chicago, IL, USA).

Study III

Logistic regression analysis was performed to assess the independent association of the metabolic syndrome and its components with diabetic nephropathy (vs. normal urinary albumin excretion). The multivariate model was adjusted for age, sex, HbA_{1c}, and smoking. The data are presented as odds ratio with 95% confidence intervals. All analyses were performed using SPSS 11.5 statistical software (SPSS Inc., Chicago, IL, USA).

Study IV

Separate Cox proportional hazard models were used for each of the definitions of the metabolic syndrome. The results are presented as hazard ratios with 95% confidence intervals. Follow-up time to the event studied was used as the time variable in the models. For analyses of the cardiovascular end-points, the models were first adjusted for traditional risk factors (gender, age, smoking, LDL-cholesterol, and HbA_{1c}), then for previous events, and finally for diabetic nephropathy. The Cox regression analyses for progression of renal disease were adjusted for duration of diabetes, gender, smoking, and HbA_{1c}. For subanalyses of the components of the metabolic syndrome, the components of one definition were analyzed in one model. To test the combined effect of the MS^{NCEP}/MS^{IDF} and albuminuria on new cardiovascular events and mortality, Kaplan-Meier survival analyses were used and statistical significance of differences was tested with Log rank test. All analyses were performed using SPSS 15.0 statistical software (SPSS Inc., Chicago, IL, USA).

Study I - Parental risk factors for nephropathy in type 1 diabetes

Parental factors associated with diabetic nephropathy were studied in 2,355 patients with type 1 diabetes. Clinical characteristics of the patients are shown in Table 3 (Section 4). Compared with patients without diabetic nephropathy, patients with diabetic nephropathy were older, had an earlier onset of diabetes, a longer duration of diabetes, higher blood pressure, and higher HbA_{1c}, as well as a lower estimated glucose disposal rate and glomerular filtration rate. Patients with diabetic nephropathy also had more coronary heart disease, stroke, and amputations. Both patients with diabetic nephropathy and their parents were older than patients without diabetic nephropathy and their parents, and therefore, the results have been adjusted for the patients' age.

Parental risk factors

The availability of parental data varied between 82% and 94% for maternal and paternal hypertension, cardiovascular disease, diabetes, and mortality. No difference was present in the data available for those with and without diabetic nephropathy (Table 6) (previously unpublished data). Of the parental factors, only hypertension and type 1 diabetes, especially in mothers, were independently associated with diabetic nephropathy in patients with type 1 diabetes, after adjustment for other parental risk factors, duration of diabetes, HbA_{1c}, and gender (Figure 4).

Clustering of parental risk factors

Figure 5 shows how the prevalence of diabetic nephropathy increased with the load of hypertension, cardiovascular disease, and diabetes, although the data did not reach statistical significance for diabetes. If both, compared with neither, of the parents had hypertension, the adjusted odds ratio for diabetic nephropathy was 1.56 (95% confidence interval 1.13-2.15). A combination of parental risk factors increased the likelihood of developing diabetic nephropathy. The odds ratios of the parental factors for diabetic nephropathy, adjusted for duration of diabetes, gender, and HbA_{1c}, are shown in Table 7.

Parental mortality

Of the 4,676 parents, 1,635 (35%) had died. The number of deceased mothers was 584; 187 (32%) died from cardiovascular disease, 148 (25%) from cancer, 129 (22%) from other causes, and for 120 mothers (21%) the cause of death was unknown. Of the 1,051 deceased fathers, 409 (39%) died from cardiovascular disease, 213 (20%) from cancer, 232 (22%) from other causes, and for 197 (19%) the cause of death was unknown. In Kaplan-Meier survival analysis, fathers of patients with diabetic nephropathy showed reduced overall survival (P = 0.037) and also reduced survival from fatal cardiovascular events (Figure 6). Kaplan-Meier curves showed no difference in maternal overall survival (P = 0.808) or survival from fatal cardiovascular events (P = 0.662).

Table 6. Available parental data for patients with and without diabetic nephropathy (n = 2,355)

	DN n = 780	No DN n = 1,575	P value
Mat. HT (%)	89	90	0.431
Mat. diabetes (%)	92	92	0.462
Mat. CVD (%)	86	88	0.314
Mat. mortality (%)	100	100	-
Pat. HT (%)	80	82	0.233
Pat. diabetes (%)	94	94	0.854
Pat. CVD (%)	81	83	0.181
Pat. mortality (%)	100	100	-

Data are percentages. DN = diabetic nephropathy, Mat. = maternal, Pat. = paternal, HT = hypertension, CVD = cardiovascular disease.

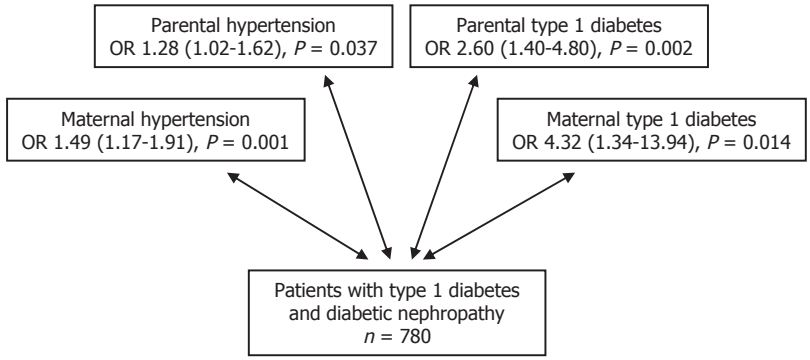
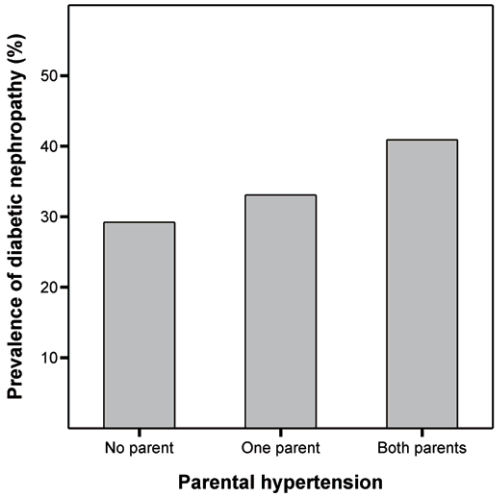


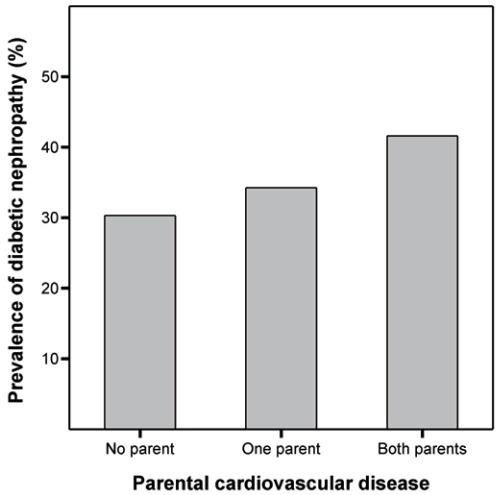
Figure 4. Parental factors independently associated with diabetic nephropathy, after adjustment for duration of diabetes, HbA1c, and gender. Parental type 2 diabetes, cardiovascular disease, and mortality were not independently associated with diabetic nephropathy.

Table 7. Adjusted odds ratio for diabetic nephropathy by parental risk factors

	Odds ratio* (95% CI)	**P value**
Parental hypertension		0.025
One parent vs. neither parent	1.13 (0.90-1.41)	0.302
Both parents vs. neither parent	1.56 (1.13-2.15)	0.007
Parental diabetes		0.660
One parent vs. neither parent	1.03 (0.83-1.29)	0.765
Both parents vs. neither parent	1.35 (0.69-2.64)	0.376
Parental cardiovascular disease		0.507
One parent vs. neither parent	0.94 (0.74-1.20)	0.637
Both parents vs. neither parent	1.21 (0.81-1.82)	0.349
Parental score of hypertension and diabetes		0.007
1 vs. 0 points	1.07 (0.84-1.37)	0.567
2 vs. 0 points	1.26 (0.94-1.69)	0.128
3-4 vs. 0 points	2.13 (1.36-3.33)	0.001
Parental score of hypertension and cardiovascular disease		0.099
1 vs. 0 points	0.99 (0.76-1.29)	0.941
2 vs. 0 points	1.23 (0.91-1.67)	0.184
3-4 vs. 0 points	1.48 (1.02-2.13)	0.037
Parental score of hypertension, cardiovascular disease, and diabetes		0.009
1 vs. 0 points	1.09 (0.83-1.45)	0.536
2-3 vs. 0 points	1.15 (0.87-1.53)	0.318
4-6 vs. 0 points	2.13 (1.37-3.33)	0.001

*Data are odds ratios with 95% confidence intervals. All parental variables were entered into the logistic regression models as categorical variables with 0 points as the reference category. Diabetes = type 1 and type 2 combined. *Adjusted for duration of diabetes, sex, and* HbA_{1c}.





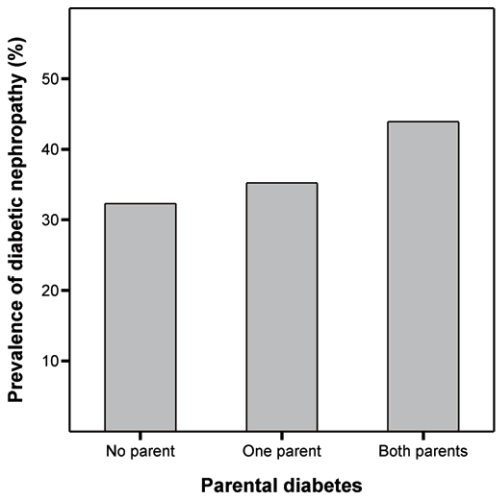


Figure 5. Frequency of diabetic nephropathy if neither, one, or both parents had hypertension (P = 0.001), cardiovascular disease (P = 0.006), either type 1 or type 2 diabetes (P = 0.075).

Study II - Effect of parental type 2 diabetes on patients with type 1 diabetes

The role of parental history of type 2 diabetes was assessed in 1,860 patients with type 1 diabetes. Table 8 shows the clinical characteristics of the patients grouped by parental history of type 2 diabetes. Patients with a positive parental history of type 2 diabetes had a higher body mass index, larger waist circumference, higher triglyceride concentrations, and higher HbA_{1c} concentrations, while no difference was observed in blood pressure or prevalence of diabetic complications. Surprisingly, patients with a positive parental history of type 2 diabetes had a later onset of type 1 diabetes (Figure 7). This association was further evaluated by the use of stricter criteria for type 1 diabetes, that is age at onset below 25 years (n = 1,465), and the results remained unchanged (age at onset 13.3 ± 6.3 vs. 12.6 ± 6.2 years, P = 0.043), but if age at onset was lowered to 15 years (n = 921) the difference in age at onset of type 1 diabetes disappeared (9.0 ± 3.8 vs. 8.8 ± 3.8 years, P = 0.411). The publicly available DCCT dataset was used as a

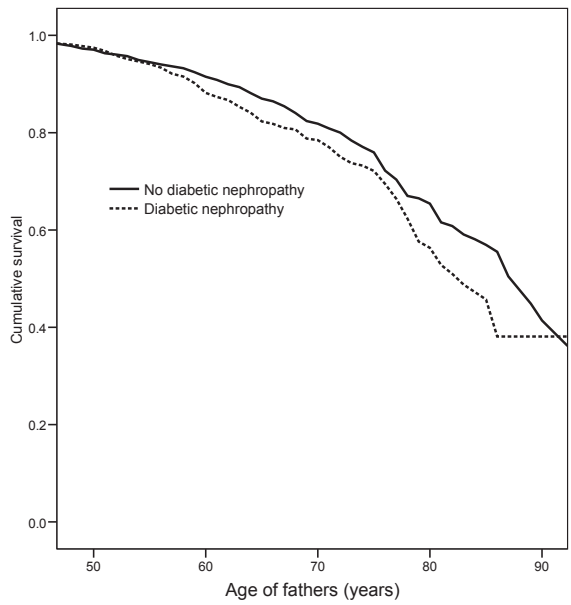


Figure 6. Kaplan-Meier survival analysis of fathers of patients with and without diabetic nephropathy, showing cumulative survival from cardiovascular death (P = 0.034).

Table 8. Clinical characteristics of patients grouped by parental history of type 2 diabetes (n = 1,860)

	Negative parental history of type 2 diabetes n = 1,240	Positive parental history of type 2 diabetes n = 620	P value	Positive maternal history of type 2 diabetes n = 327	P value	Positive paternal history of type 2 diabetes n = 248	P value
Males (%)	50	49	0.431	49	0.688	49	0.711
Age (years)	43.4 ± 10.0	43.9 ± 10.2	0.344	46.1 ± 10.1	<0.001	40.8 ± 9.7	<0.001
Age at diabetes onset (years)	16.1 ± 8.9	17.2 ± 9.0	0.008	17.8 ± 9.2	0.002	16.5 ±8.7	0.428
Duration of diabetes (years)	27.3 ± 11.7	26.6 ± 11.4	0.214	28.2 ± 11.5	0.208	24.2 ± 10.9	<0.001
Body mass index (kg/m^2)	25.0 ± 3.5	25.7 ± 3.8	<0.001	25.7 ± 3.7	0.001	25.6 ± 3.8	0.010
Waist circumference (cm)	86.1 ± 11.5	88.0 ± 12.0	0.002	88.2 ± 12.2	0.005	87.6 ± 11.8	0.066
Total cholesterol (mmol/l)	5.03 ± 0.97	5.13 ± 0.97	0.027	5.20 ± 0.99	0.003	5.04 ± 0.95	0.855
LDL-cholesterol (mmol/l)	3.10 ± 0.91	3.15 ± 0.90	0.290	3.23 ± 0.93	0.029	3.05 ± 0.86	0.451
HDL-cholesterol (mmol/l)	1.38 ± 0.44	1.37 ± 0.46	0.478	1.37 ± 0.45	0.686	1.36 ± 0.47	0.424
Triglycerides (mmol/l)	1.01 (0.75-1.39)	1.06 (0.80-1.62)	0.001	1.10 (0.81-1.63)	<0.001	1.02 (0.76-1.58)	0.160
HbA_{1c} (%)	8.3 ± 1.3	8.4 ± 1.4	0.028	8.5 ± 1.4	0.004	8.2 ± 1.4	0.727
eGDR (mg/kg$^-$/min)	5.6 (4.1-8.1)	5.3 (3.9-7.9)	0.055	5.1 (3.8-7.5)	0.004	5.9 (4.3-8.0)	0.553
Insulin dose (IU/kg)	0.65 ± 0.21	0.68 ± 0.26	0.008	0.68 ± 0.26	0.071	0.70 ± 0.26	0.005
Systolic blood pressure (mmHg)	137 ± 19	138 ± 19	0.195	139 ± 19	0.082	136 ± 20	0.771
Diastolic blood pressure (mmHg)	80 ± 10	80 ± 10	0.570	80 ± 9	0.489	79 ± 10	0.854
Antihypertensive medication (%)	49	49	0.974	52	0.439	45	0.194
Coronary heart disease (%)	7.4	9.9	0.070	12	0.005	5.8	0.376
Cardiovascular events (%)	12	13	0.442	17	0.013	7.7	0.058
Diabetic nephropathy (%)	38	40	0.297	41	0.346	38	0.981
Microalbuminuria (%)	12	13	0.510	12	0.964	15	0.135
Retinal laser treatment (%)	44	44	0.892	48	0.214	40	0.260
Smoking (%)	22	26	0.019	25	0.240	30	0.004
Metabolic syndrome IDF (%)	38	43	0.029	46	0.007	36	0.684
Metabolic syndrome NCEP (%)	38	44	0.013	44	0.030	42	0.215

Data are means ± standard deviations, medians (interquartile ranges), or percentages. eGDR = estimated glucose disposal rate, IDF = International Diabetes Federation, NCEP = The National Cholesterol Education Program Adult Treatment Panel III. P values represent comparisons with negative parental history of type 2 diabetes.

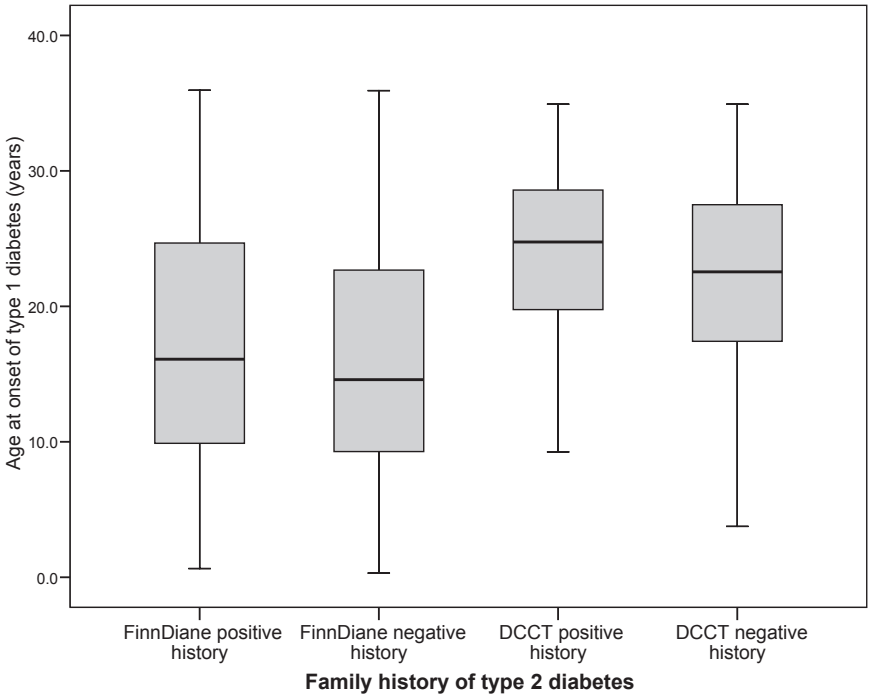


Figure 7. Age at onset of type 1 diabetes in patients with a positive, compared with those with a negative, family history of type 2 diabetes in the FinnDiane Study (17.2 ± 9.0 vs. 16.1 ± 8.9, P = 0.008) and in the DCCT cohort (23.9 ± 6.5 vs. 22.2 ± 6.8, P = 0.008).

replication set, and the results were similar (Figure 7). The association of later onset of type 1 diabetes with positive family history of type 2 diabetes in the DCCT was significant also after adjustment for body mass index, triglycerides, insulin dose, and HbA_{1c} [odds ratio 1.04 (1.01-1.07), $P = 0.013$] (previously unpublished data).

Metabolic syndrome and insulin resistance

The more components of the MS^{NCEP} that the patients fulfilled, the higher the prevalence of parental type 2 diabetes (Figure 8). The MS^{NCEP} score was associated with parental history of type 2 diabetes [5 points vs. 1 point odds ratio 2.70 (1.51-4.81), $P = 0.001$, and as a continuous score odds ratio 1.16 (1.04-1.28), $P = 0.006$], after adjustment for age at onset of diabetes, HbA_{1c}, and insulin dose. Patients with a positive parental history of type 2 diabetes also had a higher insulin dose per body weight ($P = 0.008$) and showed a tendency to be more insulin resistant, defined by a lower estimated glucose disposal rate ($P = 0.055$) (Table 8). Factors independently associated with parental history of type 2 diabetes are shown in Table 9.

Maternal and paternal history of type 2 diabetes

Patients with a positive maternal history of type 2 diabetes were older than those with a negative parental history, and those with a positive paternal history of type 2 diabetes were notably younger (Table 8). Factors independently associated with a maternal and paternal history of type 2 diabetes, after adjustment for age, are shown in Table 9. In the logistic regression model for maternal history of type 2 diabetes, estimated glucose disposal rate was excluded since waist circumference and HbA_{1c} were included in the formula for estimated glucose disposal rate. A separate analysis was performed with estimated glucose disposal rate in the model, while waist circumference and HbA_{1c} were excluded, but the estimated glucose disposal rate was not independently associated with maternal history of type 2 diabetes.

HLA haplotypes and genotypes

HLA data were available for 1,136 patients, and in these patients 23 different haplotypes were found. Haplotypes with a frequency above 1% are shown in Table 10. The DRB1*0401-DQB1*0302 and (DR7)-DQA1*0201-DQB1*02 were slightly more common among those with a positive parental history of type 2 diabetes, whereas (DR3)-DQA1*05-DQB1*02 was more common among those with a negative parental history. These differences were not significant after correction for the number of comparisons. The haplotype combinations generated 85 different HLA genotypes, and these were classified according to the conferred risk of type 1 diabetes. No difference existed in frequency with respect to high-, moderate-, and low-risk genotypes, or protective genotypes in patients with and without a parental history of type 2 diabetes. Genotypes associated with

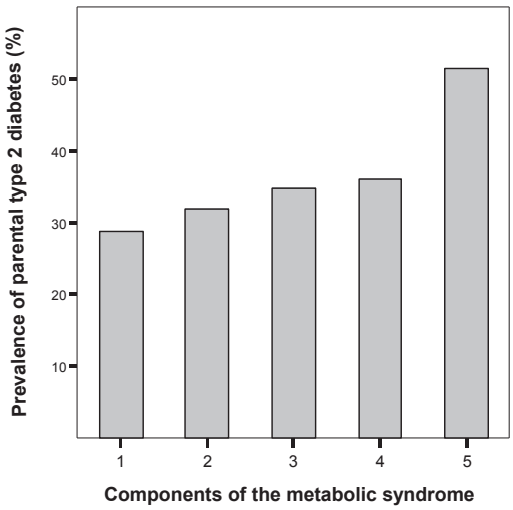


Figure 8. Frequency of parental type 2 diabetes increased with number of components of the metabolic syndrome according to the NCEP definition (P = 0.007).

Table 9. Factors independently associated with parental history of type 2 diabetes as well as with maternal and paternal type 2 diabetes

	Independent odds ratio (95% CI)	P value
Parental history of type 2 diabetes*		
Age at onset of type 1 diabetes (years)	1.02 (1.01-1.03)	0.004
Body mass index (kg/m^2)	1.07 (1.02-1.12)	0.002
Triglycerides (mmol/l)	1.18 (1.03-1.35)	0.016
Insulin dose (IU/kg)	1.63 (1.04-2.54)	0.033
Maternal history of type 2 diabetes†		
Age at onset of type 1 diabetes (years)	1.02 (1.01-1.03)	0.019
Body mass index (kg/m^2)	1.07 (1.02-1.13)	0.013
Triglycerides (mmol/l)	1.18 (1.01-1.38)	0.040
HbA_{1c} (%)	1.11 (1.01-1.22)	0.034
Insulin dose (IU/kg)	1.81 (1.02-3.23)	0.044
Paternal history of type 2 diabetes‡		
Body mass index (kg/m^2)	1.05 (1.01-1.09)	0.008
Insulin dose (IU/kg)	1.86 (1.02-3.37)	0.042

*Data are odds ratios with 95% confidence intervals. *Model also included waist circumference, HbA_{1c}, and the metabolic syndrome according to NCEP definition. †Model also included age, waist circumference, cardiovascular events, and the metabolic syndrome according to IDF definition. ‡Model also included age.*

a slightly increased risk were more common among those with a negative parental history of type 2 diabetes. The HLA genotype distribution in patients with a positive parental history of type 2 diabetes did not differ from a Finnish population of children with type 1 diabetes, but all genotypes, except those that associated with a slightly increased risk of type 1 diabetes, differed significantly from a control population without diabetes (Table 11).

Study III - The metabolic syndrome in type 1 diabetes

The prevalence of the metabolic syndrome was assessed in 2,415 patients with type 1 diabetes. Clinical characteristics of the patients with and without the metabolic syndrome are presented in Table 4 (Section 4). The prevalence of the MS^{NCEP} and its components by gender and age is shown in Tables 12 a-b. Figure 9 shows the

Table 10. Distribution of the most common HLA haplotypes (frequency >1%) in patients with type 1 diabetes and available HLA data grouped by parental history of type 2 diabetes (n = 1,136)

	Positive parental history of type 2 diabetes (haplotypes n = 776)	Negative parental history of type 2 diabetes (haplotypes n = 1,496)	P value
DRB1*0401-DQB1*0302	35	30	0.015
(DR3)-DQA1*05-DQB1*02	20	24	0.033
(DR1/10)-DQB1*0501	12	11	0.290
(DR8)-DQB1*04	7.9	7.8	0.928
DRB1*0404-DQB1*0302	7.7	10	0.059
(DR13)-DQB1*0604	2.8	4.4	0.065
(DR9)-DQA1*03-DQB1*0303	2.6	2.7	0.892
(DR7)-DQA1*0201-DQB1*02	3.6	1.9	0.011
(DR4)-DQA1*03-DQB1*0301	1.9	2.1	0.744
(DR11/12/13)-DQA1*05-DQB1*0301	2.1	1.9	0.841
(DR13)-DQB1*0603	1.8	1.9	0.824

Data are percentages of the haplotypes in each group. Copyright © 2009 American Diabetes Association From Diabetes Care®, Vol. 32; 2009, 63-68. Reprinted with permission from The American Diabetes Association.

Table 11. HLA genotypes by the risk associated with type 1 diabetes grouped by parental history of type 2 diabetes, compared with previous data for 622 Finnish children with type 1 diabetes and 622 affected family-based artificial controls [24,317].

	Negative parental history of type 2 diabetes n = 748	Positive parental history of type 2 diabetes n = 388	P value*	Finnish children with type 1 diabetes n = 622	P value†	Affected family-based artificial controls n = 622	P value‡
High-risk (%)	28	26	0.522	24	0.312	0.8	<0.001
Moderate-risk (%)	44	48	0.128	45	0.310	11	<0.001
Slightly increased risk (%)	13	8.2	0.028	12	0.077	7.6	0.691
Low-risk (%)	13	13	0.738	17	0.094	32	<0.001
Protective (%)	2.9	3.6	0.543	2.3	0.201	49	<0.001

*Data are percentages. *Comparison between negative and positive parental history of type 2 diabetes. †Comparison between positive parental history of type 2 diabetes and previous results for Finnish children with type 1 diabetes. ‡Comparison between affected family-based artificial controls and positive parental history of type 2 diabetes. Copyright © 2009 American Diabetes Association From Diabetes Care®, Vol. 32; 2009, 63-68. Reprinted with permission from The American Diabetes Association.*

distribution of the number of components fulfilled by the patients, and the different combinations of the components are displayed in Table 13.

Table 12a. Prevalence of the metabolic syndrome (MS^{NCEP}) and its components by gender (n = 2,415)

	Males n=1,241	Females n=1,174	P value
MS^{NCEP} (%)	38	40	0.448
MS^{NCEP} obesity (%)	12	20	<0.001
MS^{NCEP} hypertension (%)	76	63	<0.001
MS^{NCEP} low HDL-cholesterol (%)	28	42	<0.001
MS^{NCEP} high triglycerides (%)	24	14	<0.001

Data are percentages

Table 12b. Prevalence of the metabolic syndrome (MS^{NCEP}) and its components by age (n = 2,415)

	Age groups (years)				
	18-30 n = 727	30-40 n = 729	40-50 n = 594	>50 n = 365	P value
MS^{NCEP} (%)	33	40	41	47	<0.001
MS^{NCEP} obesity (%)	9	15	20	26	<0.001
MS^{NCEP} hypertension (%)	51	69	80	90	<0.001
MS^{NCEP} low HDL-cholesterol (%)	38	37	34	27	0.001
MS^{NCEP} high triglycerides (%)	19	20	19	17	0.753
Lipid-lowering medication (%)	0.8	6.6	14	27	<0.001

Data are percentages

Table 13. Different combinations of the components of the MS^{NCEP} in affected patients (n = 944)

	Frequency (%)
DM + HT + HDL	30
DM + HT + HDL + trigly	15
DM + HT + obesity	14
DM + HT + trigly	13
DM + HT + HDL + trigly + obesity	8.4
DM + HT + HDL + obesity	8.2
DM + HDL + trigly	3.8
DM + HT + trigly + obesity	3.6
DM + HDL + obesity	2.5
DM + HDL + trigly + obesity	0.6
DM + trigly + obesity	0.4

Data are percentages. DM = diabetes, HT = hypertension, HDL = low HDL-cholesterol, trigly = high triglycerides

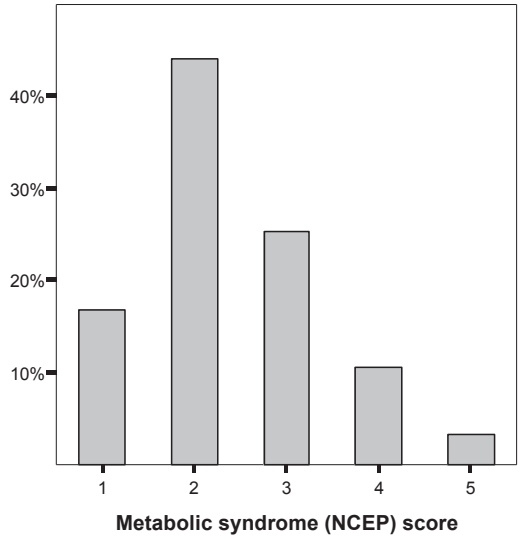


Figure 9. Distribution of the number of components of the metabolic syndrome (NCEP) fulfilled by the patients with type 1 diabetes (n = 2,415).

Table 14. Prevalence of the metabolic syndrome (MS^{NCEP}) and its components by diabetic nephropathy

	Renal status				
	Normal UAER n = 1,261	Micro n = 326	Macro n = 383	ESRD n = 164	P value
MS^{NCEP} (%)	28	44	62	68	<0.001
MS^{NCEP} obesity (%)	12	18	23	29	<0.001
MS^{NCEP} hypertension (%)	55	88	98	99	<0.001
MS^{NCEP} low HDL-cholesterol (%)	33	30	46	46	<0.001
MS^{NCEP} high triglycerides (%)	13	19	33	35	<0.001

Data are percentages. UAER = urinary albumin excretion rate, micro = microalbuminuria, macro = macroalbuminuria, ESRD = end-stage renal disease.

Diabetic nephropathy and the metabolic syndrome

Patients with the metabolic syndrome had more microvascular complications, including laser-treated retinopathy and nephropathy (Table 4). The prevalence of the metabolic syndrome increased with worsening renal disease (Table 14). After adjustment for age, gender, smoking, and HbA_{1c}, patients with the metabolic syndrome, compared with those without, had a 3.75-fold (2.89-4.85) increased odds ratio for diabetic nephropathy. Of the individual components, hypertension was by far the component associated with the strongest relationship with diabetic nephropathy [odds ratio 35.75 (18.33-69.70)], but all other components were also independently associated with diabetic nephropathy: low HDL-cholesterol [odds ratio 1.73 (1.39-2.15)], high triglycerides [2.04 (1.60-2.60)], and abdominal obesity [1.38 (1.07-1.79)] (unpublished results). Compared with patients fulfilling 1 or 2 components, the odds ratio for diabetic nephropathy increased for every added component: 3 components 2.81 (2.09-3.78), 4 components 5.09 (3.45-7.50), and all 5 components 11.70 (5.74-23.84).

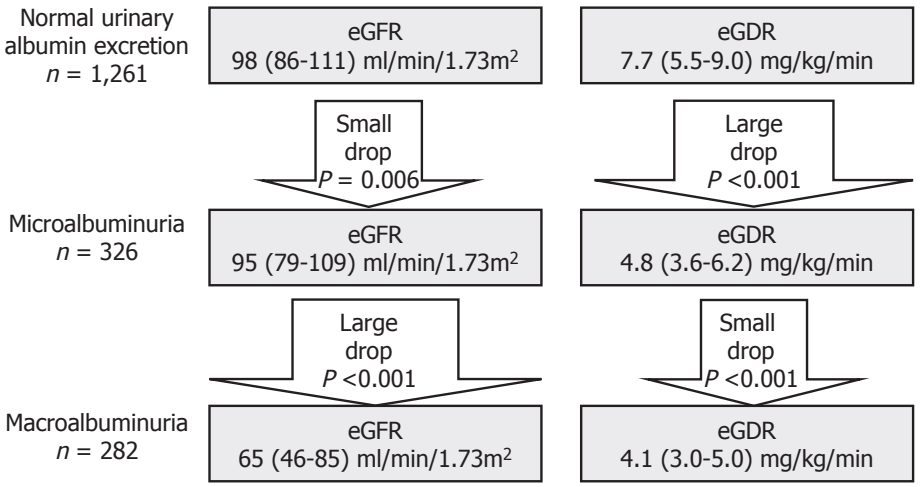


Figure 10. Renal function (eGFR) and insulin sensitivity (eGDR) in different stages of albuminuria.

Table 15. Prevalence of the metabolic syndrome (MS^{NCEP}) and its components by HbA_{1c} (n = 2,360)

	HbA_{1c} (%)			P value
	<7.5 n = 578	7.5-9.0 n = 1,087	>9.0 n = 695	
MS^{NCEP} (%)	31	36	51	<0.001
MS^{NCEP} obesity (%)	10	16	21	<0.001
MS^{NCEP} hypertension (%)	60	71	76	<0.001
MS^{NCEP} low HDL-cholesterol (%)	34	33	40	0.010
MS^{NCEP} high triglycerides (%)	13	16	28	<0.001

Data are percentages

Effect of renal function and insulin sensitivity

Most patients with type 1 diabetes with normal urinary albumin excretion and renal function had normal insulin sensitivity. However, patients with microalbuminuria were more insulin resistant, while decreased renal function was a conspicuous feature in those with macroalbuminuria, suggesting that insulin resistance precedes the decline in renal function (Figure 10).

Glycemic control and the metabolic syndrome

The prevalence of the metabolic syndrome increased with worsening glycemic control (Table 15). This association was seen in patients with normal urinary albumin excretion, macroalbuminuria, and end-stage renal disease, but was less clear in patients with microalbuminuria (Figure 11).

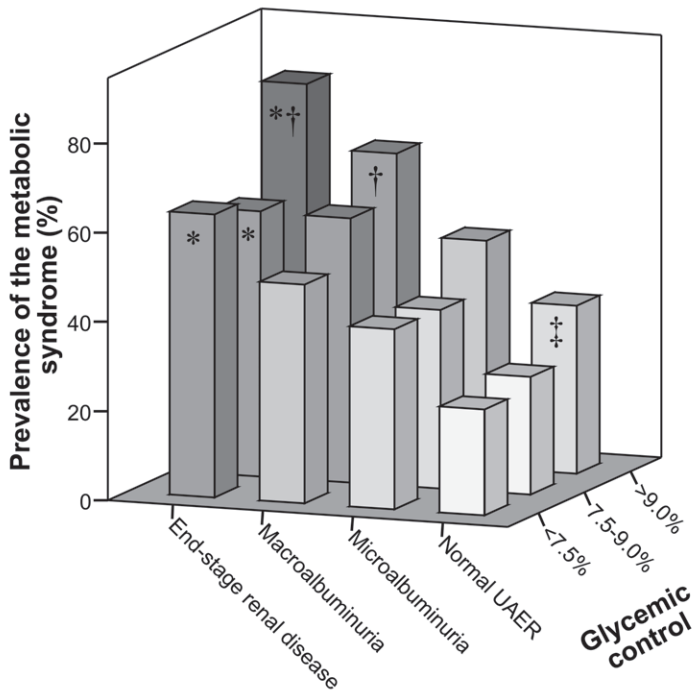


Figure 11. Frequency of the metabolic syndrome according to glycemic control and different stages of albuminuria. UAER = urinary albumin excretion rate. *P <0.001 within the HbA1c groups, †P <0.001 within the groups of albuminuria, ‡P <0.05 within the groups of albuminuria.

Table 16. Hazard ratios (HRs) for cardiovascular outcomes and cardiovascular and diabetes-related mortality by different criteria for the metabolic syndrome

	MS^{WHO} HR (95% CI)	P value	MS^{NCEP} HR (95% CI)	P value	MS^{IDF} HR (95% CI)	P value
New cardiovascular event (n = 263)	5.73 (4.14-7.92)	<0.001	2.45 (1.92-3.14)	<0.001	1.66 (1.30-2.11)	0.001
adjusted for traditional risk factors*	3.65 (2.59-5.14)	<0.001	1.89 (1.46-2.46)	0.001	1.09 (0.84-1.41)	0.535
further adjusted for previous cardiovascular event	2.98 (2.10-4.24)	<0.001	1.64 (1.23-2.14)	<0.001	1.03 (0.79-1.33)	0.833
further adjusted for diabetic nephropathy	2.05 (1.38-3.04)	<0.001	1.31 (0.99-1.72)	0.056	0.96 (0.74-1.25)	0.759
New myocardial infarction (n = 161)	10.29 (6.14-17.25)	<0.001	2.61 (1.90-3.59)	<0.001	1.76 (1.29-2.39)	<0.001
adjusted for traditional risk factors*	6.30 (3.68-10.78)	<0.001	1.85 (1.32-2.59)	<0.001	1.16 (0.83-1.62)	0.375
further adjusted for previous myocardial infarction	5.80 (3.38-9.97)	<0.001	1.67 (1.19-2.35)	0.003	1.11 (0.79-1.54)	0.558
further adjusted for diabetic nephropathy	3.10 (1.70-5.68)	<0.001	1.17 (0.83-1.65)	0.380	1.00 (0.72-1.40)	0.992
New stroke (n = 80)	7.51 (3.86-14.60)	<0.001	1.94 (1.25-3.02)	0.003	1.10 (0.70-1.73)	0.684
adjusted for traditional risk factors*	4.86 (2.42-9.77)	<0.001	1.51 (0.94-2.44)	0.090	0.73 (0.45-1.20)	0.218
further adjusted for previous stroke	4.49 (2.22-9.07)	<0.001	1.45 (0.89-2.34)	0.133	0.65 (0.40-1.08)	0.096
further adjusted for diabetic nephropathy	2.81 (1.29-6.15)	0.010	1.05 (0.64-1.71)	0.859	0.66 (0.40-1.07)	0.093
Cardiovascular and diabetes-related mortality (n = 238)	11.05 (7.25-16.85)	<0.001	2.87 (2.21-3.73)	<0.001	1.79 (1.39-2.31)	<0.001
adjusted for traditional risk factors*	7.33 (4.69-11.46)	<0.001	2.15 (1.63-2.84)	<0.001	1.20 (0.92-1.58)	0.185
further adjusted for diabetic nephropathy	2.52 (1.53-4.16)	<0.001	1.31 (0.99-1.73)	0.063	1.00 (0.76-1.32)	0.986

*Data are hazard ratios with 95% confidence intervals. *Age, gender, smoking, LDL-cholesterol, and HbA_{1c}. MS^{WHO} = metabolic syndrome according to World Health Organization, MS^{NCEP} = National Cholesterol Education Program Adult Treatment Panel III, MS^{IDF} = International Diabetes Federation*

Table 17. Independent effect of individual components of the metabolic syndrome for cardiovascular events and mortality

	New cardiovascular events adj HR (95% CI)*	P value	Cardiovascular or diabetes-related mortality adj HR (95% CI)*	P value
MS^{WHO}				
MS^{WHO} elevated UAER	2.69 (1.95-3.72)	<0.001	10.32 (6.28-16.96)	<0.001
MS^{WHO} obesity	1.28 (0.97-1.68)	0.080	1.23 (0.92-1.66)	0.170
MS^{WHO} hypertension	1.71 (1.26-2.31)	<0.001	1.69 (1.23-2.31)	0.001
MS^{WHO} dyslipidemia	1.80 (1.38-2.35)	<0.001	2.11 (1.60-2.78)	<0.001
MS^{NCEP}				
MS^{NCEP} obesity	0.94 (0.68-1.30)	0.722	0.99 (0.71-1.37)	0.938
MS^{NCEP} hypertension	2.00 (1.36-2.39)	<0.001	2.04 (1.37-3.04)	<0.001
MS^{NCEP} low HDL-cholesterol	1.35 (1.03-1.78)	0.031	1.43 (1.07-1.91)	0.016
MS^{NCEP} high triglycerides	1.83 (1.35-2.48)	<0.001	2.29 (1.68-3.12)	<0.001
MS^{IDF}				
MS^{IDF} obesity	0.82 (0.63-1.06)	0.132	0.84 (0.63-1.11)	0.212
MS^{IDF} hypertension	4.25 (2.28-7.92)	<0.001	5.47 (2.66-11.26)	<0.001
MS^{IDF} low HDL-cholesterol	1.63 (1.24-2.13)	<0.001	1.47 (1.10-1.96)	0.009
MS^{IDF} high triglycerides	1.76 (1.31-2.37)	<0.001	2.32 (1.70-3.15)	<0.001

*Data are hazard ratios with 95% confidence intervals. *Adjusted for age, gender, smoking, LDL-cholesterol, and HbA_{1c}. MS^{WHO} = metabolic syndrome according to World Health Organization, UAER = urinary albumin excretion rate, MS^{NCEP} = National Cholesterol Education Program Adult Treatment Panel III, MS^{IDF} = International Diabetes Federation*

Study IV - The metabolic syndrome as a predictor for diabetic complications in type 1 diabetes

The predictive role of the metabolic syndrome was assessed in 3,783 patients with type 1 diabetes. The metabolic syndrome was assessed according to the MS^{WHO}, MS^{NCEP}, and MS^{IDF}. Detailed clinical characteristics of the patients are presented in Table 5 (Section 4). The overlap between the different definitions is shown in Figure 12. Presence of the MS^{WHO} was observed in 44%, MS^{NCEP} in 35%, and MS^{IDF} in 36% of the patients.

Cardiovascular events

The median follow-up time was 5.5 (interquartile range 3.7-6.7) years, and 263 patients suffered a cardiovascular event, 106 (40%) of whom had a history of cardiovascular events. Of those who suffered a new cardiovascular event, 161 had a myocardial infarction [31 (19%) with a history of myocardial infarction], and 80 a stroke [12 (15%) with a history of stroke]. The predictive value of MS^{WHO}, MS^{NCEP}, and MS^{IDF} for the different cardiovascular outcomes is shown in Table 16. Of the individual components of the metabolic syndrome, all except obesity were independent predictors of cardiovascular events (Table 17).

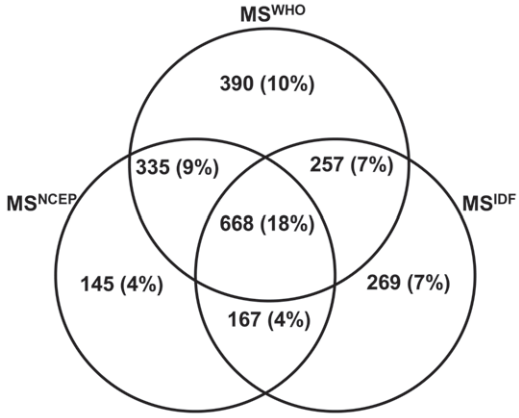


Figure 12. Overlap between the different definitions of the metabolic syndrome. Copyright © 2009 American Diabetes Association From Diabetes Care®, Vol. 32; 2009, 950-952. Reprinted with permission from The American Diabetes Association.

Table 18. Mortality by different levels of diabetic nephropathy

	Mortality (%)	Proportion of deaths from cardiovascular or diabetes-related causes (%)
Normal urinary albumin excretion rate	1.5	56
Microalbuminuria	5.9	75
Macroalbuminuria	17	84
End-stage renal disease	51	94
Unclassified renal status	2.8	57

Data are percentages

Mortality

A total of 285 patients died during a median follow-up time of 5.7 (4.0-6.9) years. The most common cause of death was from cardiovascular disease (n = 160, 56%), and altogether 238 (84%) died from either cardiovascular or diabetes-related causes, while 13 (5%) died from cancer, eight (3%) from accidents, six (2%) committed suicide, and 20 (7%) died from unknown or other causes. The mortality rate was highest in patients with diabetic nephropathy and the proportion of patients who died from cardiovascular or diabetes-related causes increased with the severity of renal disease (Table 18). The predictive value of the metabolic syndrome for cardiovascular and diabetes-related mortality is shown in Table 16. Of the individual components of the metabolic syndrome, all except obesity were independent predictors of cardiovascular and diabetes-related mortality (Table 17).

Combination of albuminuria with the MS^{NCEP} and MS^{IDF} definitions

Since MS^{WHO}, which is the only definition that includes microalbuminuria, was the strongest

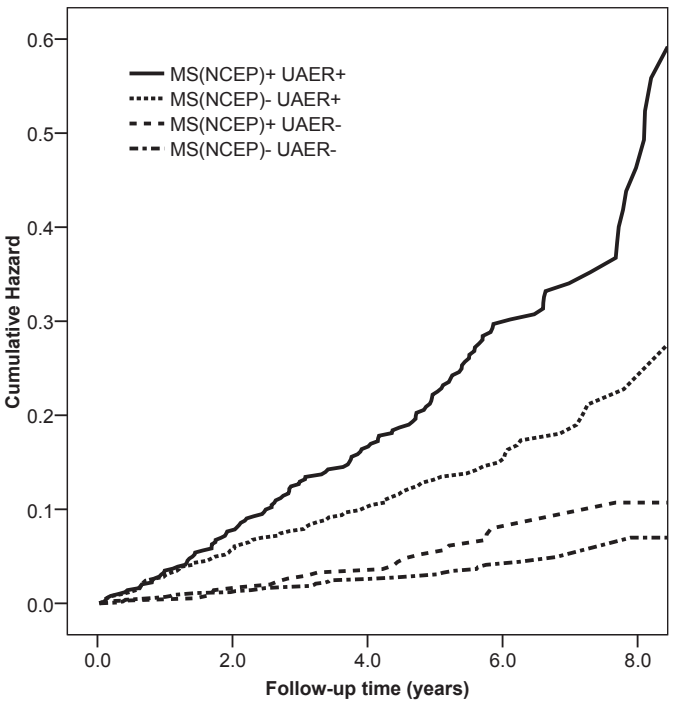


Figure 13a.

Cumulative hazard of cardiovascular events. MS(NCEP)+ = metabolic syndrome according to NCEP definition, UAER+ = urinary albumin excretion rate ≥20 µg/min or ≥30 mg/24h. Difference between MS(NCEP)+ UAER- and MS(NCEP)- UAER- P = 0.061, difference between all other groups P <0.001.

predictor of cardiovascular morbidity and cardiovascular and diabetes-related mortality, the role of albuminuria was further evaluated by combining albuminuria (≥20 µg/min or ≥30 mg/24h) with MS^{NCEP}. MS^{NCEP} added to the risk attributed to albuminuria for both cardiovascular events (Figure 13a) and cardiovascular and diabetes-related mortality (Figure 13b). In those with an elevated urinary albumin excretion rate, MS^{NCEP} was associated with a 1.44 (1.06-1.96) hazard ratio for a new cardiovascular event, after adjustment for traditional risk factors and diabetic nephropathy. Even though very few events occurred in those with a normal urinary albumin excretion rate, there was still a tendency towards more cardiovascular events in those with the metabolic syndrome (MS^{NCEP}) (Figure 13a). MS^{IDF} did not add to the risk attributed to an elevated urinary albumin excretion rate (P = 0.175), but in those with a normal urinary albumin excretion rate, MS^{IDF} increased the risk for cardiovascular events (P = 0.018). Regarding cardiovascular and diabetes-related mortality, MS^{IDF} did not alter the risk attributed to an elevated or normal urinary albumin excretion rate (P = 0.075 and P = 0.794, respectively).

Progression of renal disease

During follow-up, 118 patients with normal urinary albumin excretion at baseline developed microalbuminuria, 54 with microalbuminuria developed macroalbuminuria, and 130 with macroalbuminuria developed end-stage renal disease. The hazard ratios of the metabolic syndrome and its components for progression of diabetic nephropathy are presented in Table 19. MS^{WHO} predicted progression to microalbuminuria, while MS^{NCEP} and MS^{IDF} did not, and none of the three definitions predicted progression to macroalbuminuria. Regarding progression from macroalbuminuria to end-stage renal disease, MS^{WHO} and MS^{NCEP} were both significant predictors, while MS^{IDF} seemed to be protective. The seemingly protective role of MS^{IDF} was largely due to MS^{IDF} obesity, the only one of the components to show a potential protective role.

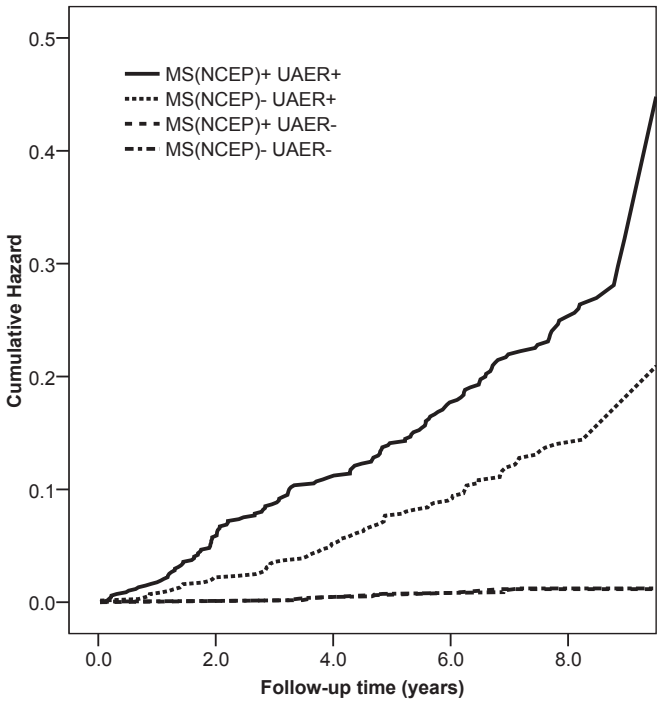


Figure 13b.

Cumulative hazard of cardiovascular and diabetes-related mortality. MS(NCEP)+ = metabolic syndrome according to NCEP definition, UAER+ = urinary albumin excretion rate ≥20 µg/min or ≥30 mg/24h. Difference between MS(NCEP)+ UAER- and MS(NCEP)- UAER- P = 0.928, difference between all other groups P <0.001.

Table 19. Hazard ratios (HRs) for progression of diabetic nephropathy by different definitions of the metabolic syndrome and their components

	Progression to microalbuminuria adjusted HR (95% CI)*	P value	Progression to macroalbuminuria adjusted HR (95% CI)*	P value	Progression to end-stage renal disease adjusted HR (95% CI)*	P value
MS^{WHO}	2.10 (1.42-3.12)	<0.001	2.42 (0.96-6.12)	0.062	2.57 (1.13-5.86)	0.025
MS^{WHO} elevated UAER	5.73 (3.64-9.02)	<0.001	-		-	
MS^{WHO} obesity	1.50 (1.01-2.21)	0.044	1.24 (0.68-2.25)	0.482	0.74 (0.51-1.07)	0.105
MS^{WHO} hypertension	1.23 (0.81-1.86)	0.336	1.40 (0.80-2.45)	0.233	2.35 (1.52-3.63)	<0.001
MS^{WHO} dyslipidemia	0.81 (0.51-1.28)	0.356	2.02 (1.11-3.70)	0.022	1.99 (1.38-2.86)	<0.001
MS^{NCEP}	1.13 (0.77-1.68)	0.531	1.57 (0.91-2.71)	0.102	1.65 (1.13-2.40)	0.009
MS^{NCEP} obesity	1.03 (0.58-1.84)	0.921	1.19 (0.58-2.46)	0.630	0.49 (0.30-0.79)	0.003
MS^{NCEP} hypertension	1.21 (0.82-1.79)	0.331	0.76 (0.40-1.47)	0.418	2.08 (1.21-3.60)	0.009
MS^{NCEP} low HDL-cholesterol	0.79 (0.52-1.21)	0.283	0.61 (0.33-1.16)	0.131	1.44 (0.98-2.13)	0.066
MS^{NCEP} high triglycerides	1.42 (0.88-2.28)	0.152	3.18-1.74-5.83)	<0.001	2.05 (1.38-3.04)	<0.001
MS^{IDF}	1.30 (0.88-1.92)	0.191	1.65 (0.93-2.92)	0.085	0.52 (0.36-0.75)	<0.001
MS^{IDF} obesity	1.23 (0.82-1.83)	0.318	1.16 (0.64-2.10)	0.629	0.39 (0.26-0.57)	<0.001
MS^{IDF} hypertension	1.19 (0.80-1.77)	0.398	1.86 (0.63-5.44)	0.260	1.48 (0.36-6.06)	0.587
MS^{IDF} low HDL-cholesterol	1.00 (0.67-1.48)	0.995	1.04 (0.58-1.87)	0.886	1.60 (1.07-2.40)	0.022
MS^{IDF} high triglycerides	1.29 (0.81-2.08)	0.289	2.56 (1.37-4.77)	0.003	2.27 (1.53-3.38)	<0.001

*Data are hazard ratios with 95% confidence intervals. *Adjusted for duration of diabetes, gender, smoking, and HbA_{1c}. UAER = urinary albumin excretion rate. MS^{WHO} = metabolic syndrome according to World Health Organization, MS^{NCEP} = National Cholesterol Education Program Adult Treatment Panel III, MS^{IDF} = International Diabetes Federation.*

7 DISCUSSION

Strengths and weaknesses of the studies

All patients in Studies I to IV were part of the FinnDiane Study, a prospective study of Finnish patients with type 1 diabetes. The study population includes 15 to 20% of the adult patients with type 1 diabetes in Finland, and although the study is not population-based, it is fairly representative of patients with type 1 diabetes in Finland. The geographical distribution of the patients is similar to that of the general distribution of people in Finland (Figure 2). Patients with type 1 diabetes are usually followed at hospitals by specialists, such as endocrinologists or nephrologists. In recent years, due to lack of resources, the health care of many young patients without diabetic complications has however, been transferred to primary health care units. The majority of the FinnDiane Study centers are hospitals, and all central and university hospitals in Finland are part of the study, while only 11% of the 270 primary health care units are taking part in the enrollment of patients. In addition, the FinnDiane Study has had a special focus on the enrollment of patients with renal involvement. These facts could result in an overrepresentation of patients with diabetic complications in the FinnDiane Study, compared with the general type 1 diabetes population in Finland.

The FinnDiane Study population is undoubtedly well characterized regarding medical history and the presence of diabetic complications. At the baseline visit, anthropometric data are collected, blood samples drawn, and a urine collection performed.

Classification of renal status. The classification of diabetic nephropathy status is based on three consecutive timed urine collections and on the clinical view of the patient's attending physician, thus representing a robust classification. In Study I, patients were classified based on their renal status as having or not having diabetic nephropathy. Patients without diabetic nephropathy, that is those with a normal albumin excretion rate, were required to have diabetes for more than 15 years to ensure normal renal status. Since the incidence peak of diabetic nephropathy occurs 15 to 20 years after the onset of diabetes [7], patients with a shorter duration may still develop diabetic nephropathy later. One could argue that a bias occurs in requiring a limit in one group, but not in the other; however, only 11 patients with diabetic nephropathy had diabetes duration of less than 15 years. The same cut-off of diabetes duration of 15 years is used in many genetic studies to classify patients as having normal renal status [137]. Regarding the classification of diabetic nephropathy, overt disease was required, with either end-stage renal disease or urinary albumin excretion rate in the macroalbuminuria range.

Classification of other diabetic complications. The classification of diabetic retinopathy is not as exact as for nephropathy, being based solely on the information of whether or not retinal laser treatment has been performed. This does not reveal the severity of the disease or whether the laser treatment has been performed due to proliferative retinopathy or to macular edema. The data have, however, been validated in a subset of patients with more accurate ophthalmic data available, and in 85% the laser treatment was performed because of proliferative retinopathy (based on personal communication with Kustaa Hietala). Regarding cardiovascular disease, the events were verified from medical files and included clinically verified myocardial infarction and stroke, as well as history of coronary revascularization and amputations. Regarding the diagnosis of coronary heart disease, pharmacological treatment with long-acting nitroglycerin was also included in the definition, and thus, this definition may be considered less specific.

Definition of the metabolic syndrome. None of the current definitions available for the metabolic syndrome have taken into consideration patients with type 1 diabetes. The most widely used definitions at the time of Study III were MS^{WHO} and MS^{NCEP} [245,247]. We chose to use the MS^{NCEP} when we introduced the concept of the metabolic syndrome in patients with type 1 diabetes, since MS^{WHO} already includes albuminuria as one of the components. We argued that the combination of albuminuria, hypertension, and diabetes (= diabetic nephropathy) would already result in a diagnosis of the syndrome, and since the aim of Study III was to assess the association between the metabolic syndrome and diabetic nephropathy, the task would have been difficult using the MS^{WHO} definition. The MS^{IDF} was introduced in 2005 [249], and thus also used in the Study IV, along with MS^{NCEP} and the MS^{WHO}, which at that time had also been used in other studies on the metabolic syndrome in patients with type 1 diabetes [319-321]. All patients with type 1 diabetes were considered to fulfill the criteria for hyperglycemia, consistent with earlier studies of type 2 diabetes [16].

Insulin sensitivity. A direct measure of insulin sensitivity by the euglycemic hyperinsulinemic clamp technique would have been the most accurate way of measuring insulin sensitivity. This was, however, not feasible in this large study cohort, and thus, an estimation of the glucose disposal rate was used [179]. This estimation was originally validated in 24 patients with type 1 diabetes, only 5 of whom had antihypertensive medication. How well this formula correlates with insulin sensitivity in patients with diabetic nephropathy is unknown, but to date the estimated glucose disposal rate is the only available estimate of insulin resistance in patients with type 1 diabetes.

Parental data. In Studies I and II, information on parents was received from the patients with type 1 diabetes through a questionnaire, and not directly from the parents themselves. An optimal approach would of course have been to study all parents as well, but this was not feasible in this large cohort. The parental data was, however, validated, and showed a 83% sensitivity in detecting parental hypertension, diabetes, and cardiovascular disease. Additional limitations were that parental data in Study I were not complete and less information was available on deceased parents. Another issue with regard to parental data is undiagnosed type 2 diabetes, which European studies have shown to account for approximately 50% of all diabetes [1]. Since the parents were not themselves studied, we had no means of detecting undiagnosed type 2 diabetes in these individuals.

Matching for age. In Study II, assessment of the effect of parental history of type 2 diabetes on the patients with type 1 diabetes was performed in a subset of age-matched patients. Matching of the population for age was favored due to the large age difference between those with and those without a parental history of type 2 diabetes [43.9 ± 10.2 (n = 620) vs. 36.0 ± 11.5 years (n = 2,417)]. With such a large age difference, adjustment for age in the statistical analyses would likely not have entirely compensated the biological difference between the groups. Post-hoc analyses were performed with the entire study population, but with such a large age difference, the univariate results were unclear. More positive associations were found, and for the results presented in Table 8, after simple age adjustment, all continuous variables were significant (P <0.001). Importantly, despite the differences in univariate analyses, the results in multivariate analyses would largely have been the same, with triglycerides 1.16 (1.03-1.30), body mass index 1.05 (1.02-1.08), and age of diabetes onset 1.01 (1.01-1.03) independently associated with parental history of type 2 diabetes. Compared with the matched population, only the insulin dose per body weight, a surrogate marker of insulin sensitivity, would not have remained in the model.

Follow-up data. Follow-up data have been collected in the FinnDiane Study since 2004, and is ongoing with the goal to re-examining all patients who have participated in *phase I*. In

Studies I to III, prospective data were not yet available, and thus the studies represent only cross-sectional data. In Study IV prospective data were, however, available and used. The follow-up data are complete regarding mortality, and these data are based on death certificates, which is the method of choice. Regarding data on cardiovascular and renal morbidity, the collection of follow-up data is ongoing. Thus, in Study IV, follow-up data on cardiovascular and/or renal morbidity were available for only a subset of 69% of the patients. The morbidity data were based on a follow-up visit that included a thorough clinical examination for 36% of the patients, whereas the data were based on review of medical files for 64% of the patients. The review of medical files is done one study center at a time, thus including complete data for each study center, diminishing the bias related to the collection of follow-up data. Generally, patients for whom we lack follow-up data on morbidity are those who participated in *phase I* at a later stage, and due to a rather short follow-up time, will be restudied later. No difference was present in gender, age, or duration of diabetes in those with and without available data on morbidity at follow-up. However, those without follow-up data have a somewhat lower prevalence of diabetic complications, such as diabetic nephropathy, retinal laser treatment, and cardiovascular events, as well as a lower prevalence of the metabolic syndrome according to MS^{WHO} and MS^{NCEP}, but not MS^{IDF}. It is noteworthy that although morbidity data were available for only 69% of the patients, a significant number of cardiovascular events occurred in these patients during the 5.5-year follow-up, highlighting the clinical relevance of these data.

Which parental factors play a role in diabetic nephropathy?

In Study I, parental risk factors for diabetic nephropathy were assessed in a large cohort of patients with type 1 diabetes. Results showed that parental factors play a role in diabetic nephropathy. Notably, parental hypertension was the factor most strongly associated with diabetic nephropathy, while neither parental cardiovascular disease nor type 2 diabetes was not independently associated, but a cluster of all these traits was significantly associated with nephropathy.

The association between parental hypertension and diabetic nephropathy was driven by maternal hypertension. Although paternal hypertension was not independently associated with diabetic nephropathy, the association was stronger if both parents had hypertension. Viberti *et al.* were the first to show higher blood pressure in parents of 17 patients with type 1 diabetes and proteinuria, compared with 17 patients with normal albumin excretion rate [110]. As seen in Table 1, several studies have replicated this finding [111-119], although no association has also been observed in some large studies [121,122,124]. Only one small study assessed the separate role of maternal and paternal history of hypertension and reported higher blood pressure in mothers of patients with diabetic nephropathy [130]. In Study I, hypertension was the strongest of the parental risk factors, suggesting that a genetic predisposition to hypertension is important in the pathogenesis of diabetic nephropathy.

Parental type 1 diabetes was also independently associated with diabetic nephropathy, and this novel finding has not been reported in other studies. The prevalence of type 1 diabetes was, however, rather low. Rudberg *et al.* showed no association between parental type 1 diabetes and microalbuminuria in patients with type 1 diabetes [117], and Monti *et al.* more recently also failed to find any association between parental type 1 diabetes and self-reported diabetic nephropathy in a large study of patients with type 1 diabetes [322]. One explanation for the discrepant results could be the different methodologies applied. This is true for both the definition of diabetic nephropathy and the definition of type 1 diabetes in parents. Rudberg *et al.* defined nephropathy as a urinary albumin excretion rate of ≥15 μg/min, which means microalbuminuria

or high normal albumin excretion, and found through a questionnaire a high prevalence of type 1 diabetes in parents (11%). Monti *et al.* had a large data set with much missing data, and the parental information was received by questionnaire as well. In Study I, we were unable to classify the type of parental diabetes in 12% of parents with diabetes. The other two studies do not report how they classified the type of diabetes in the parents. Another issue is that none of these three studies had information on the nephropathy status in parents with type 1 diabetes, and thus, it cannot be ruled out that the association with parental type 1 diabetes is driven by parental diabetic nephropathy.

Parental cardiovascular morbidity was not independently associated with diabetic nephropathy. This is in line with other studies that observed no association between nephropathy and morbidity alone, but detected an association using a combined end-point of cardiovascular morbidity and mortality [114,125]. In our study, parental mortality from cardiovascular disease was associated with diabetic nephropathy, especially in fathers.

Previous studies have shown contradictory results regarding the association between parental type 2 diabetes and diabetic nephropathy [114-118,120,123,127,128], but two more recent large-scale studies have revealed associations between nephropathy and parental type 2 diabetes [124,322]. Although parental type 2 diabetes *per se* was not independently associated with diabetic nephropathy in our study, the cluster of hypertension, type 2 diabetes, and cardiovascular disease was associated with a higher risk of nephropathy. This could indicate that a common factor behind these three entities, for example insulin resistance, might be of greater importance than hypertension, cardiovascular disease, and diabetes alone.

Overall, the associations between parental factors and diabetic nephropathy in Study I were less pronounced than in some studies from the late 1980's and the beginning of the 1990's. One explanation is that treatment could affect the phenotypes of both the patients with diabetes as well as their parents. Over the last decade, treatment of patients with diabetic nephropathy has improved, and along with this also the prognosis of patients [78]. Patients with diabetes are treated with renoprotective agents to postpone or even prevent the development of diabetic nephropathy, an action that might result in patients with a genetic predisposition to diabetic nephropathy to remain in the group of patients without diabetic nephropathy. The worldwide obesity epidemic and the subsequent increase in the incidence and prevalence of type 2 diabetes [323], could also dilute the parental data, such that the type 2 diabetes observed in parents today may be due to genes to a lesser degree and to environmental factors to a higher degree. Since no clear association between parental type 2 diabetes and diabetic nephropathy was observed, the significance of parental history of type 2 diabetes for the patient with type 1 diabetes was further explored in Study II.

What is the consequence of family history of type 2 diabetes for patients with type 1 diabetes?

Little is known about the consequence of parental history of type 2 diabetes for patients with type 1 diabetes. This issue was addressed in Study II, where the impact of parental history of type 2 diabetes was assessed in a cohort of patients with type 1 diabetes, matched for age and gender. Parental history of type 2 diabetes was associated with a later onset of type 1 diabetes, a higher prevalence of the metabolic syndrome, and a metabolic profile related to insulin resistance.

In patients with, compared with those without, a parental history of type 2 diabetes, the finding of a later onset of type 1 diabetes was surprising, given the similar distribution of high-risk HLA genotypes in these two patient groups. High-risk HLA genotypes explain a substantial proportion of the genetic predisposition to type

1 diabetes and are rarely seen in patients with type 2 diabetes [324]. The distribution of HLA genotypes observed in Study II is also similar to the Finnish pediatric reference population shown in Table 11, and speaks in favor of a true type 1 diabetes population. With equal genetic predisposition, one would, in line with *the accelerator hypothesis,* expect that patients with a parental history of type 2 diabetes would have an increased risk of accelerated loss of β-cell function, and consequently, a lower age at onset of type 1 diabetes. In nondiabetic offspring, a parental history of type 2 diabetes results in insulin resistance and a higher prevalence of obesity [11,12], factors that in *the accelerator hypothesis* are assumed to be the underlying cause for accelerated β-cell loss. Notably, the association between parental history of type 2 diabetes and later onset of type 1 diabetes was replicated in the DCCT, which strengthens the observation, although it seems to be confined to patients with age at onset above 15 years.

Furthermore, in Study II, patients with a positive parental history of type 2 diabetes had a higher body mass index, larger waist circumference, higher triglyceride concentration, marginally higher HbA_{1c}, and higher insulin dose per body weight. Of these, body mass index, triglycerides, and insulin dose per body weight showed independent relationships with parental type 2 diabetes, reflecting a worse metabolic profile and suggesting the presence of insulin resistance. Other studies with the same design are not available, and it is of note that previous studies have mainly addressed the role of parental type 2 diabetes with respect to the presence of diabetic complications. They have furthermore only reported univariate data and in a descriptive manner. In these studies, a parental history of type 2 diabetes was associated with various lipid disturbances [62,128], while results regarding other metabolic variables, such as glycemic control, insulin dose, hypertension, and obesity, have shown conflicting results [62,116,118,128,325].

In type 2 diabetes, an excessive maternal transmission of diabetes occurs, and the effect on the metabolic profile of offspring without diabetes seems to be worse if the mother, rather than the father, has type 2 diabetes [61]. This issue was also addressed in Study II, and the results indicated a worse metabolic profile, and a higher prevalence of cardiovascular events in those with a history of maternal type 2 diabetes. There was, however, a more than 5-year age difference between those with a history of maternal type 2 diabetes and those with a history of paternal diabetes. The biological significance of such a large age difference might not be appropriately controlled for by adjustment for age in the statistical analyses, and thus, the results should be interpreted with caution.

What is inherited from parents with type 2 diabetes?

Is it insulin resistance or β-cell dysfunction that is inherited? Insulin resistance is thought to be an underlying condition in type 2 diabetes, while β-cell dysfunction is required for the disease to manifest. Recent results from genome-wide association studies for type 2 diabetes highlight the importance of β-cell dysfunction in the pathogenesis of type 2 diabetes. Most of the genes identified are related to decreased insulin secretory capacity and cell-cycle dysregulation [326-328]. The gene most strongly associated with type 2 diabetes is TCF7L2, a transcription factor involved in the Wnt signaling pathway. TCF7L2 is thought to be involved in impaired insulin secretion, via a decreased stimulatory effect of the incretin hormones, glucagon-like peptide-1 and gastric inhibitory polypeptide, on insulin secretion [329]. It can be argued that if genes involved in β-cell dysfunction are more important than genes involved in insulin resistance, one would expect little or no effect of parental type 2 diabetes on the metabolic phenotype of patients with type 1 diabetes. Although less genes directly involved in insulin resistance have been found so far, it is noteworthy that insulin resistance clearly clusters in families of type 2 diabetes, due to both genetic and envi-

ronmental factors, such as obesity and a sedentary lifestyle [11]. Our study design does not provide an answer to whether it is the genetic effect or the environmental effect of parental type 2 diabetes that is more important in patients with type 1 diabetes with regard to metabolic profile or presence of indicators of insulin resistance.

One interesting point that may dilute our data is that the form of type 2 diabetes seen in parents of patients with type 1 diabetes might represent a different kind of disease than type 2 diabetes in general. This hypothesis is supported by the observation of a higher proportion of glutamate decarboxylase antibodies and high-risk HLA genotypes in patients with type 2 diabetes from families with a mix of type 1 and type 2 diabetes [324]. In Study II, we unfortunately did not have data on HLA genotypes or glutamate decarboxylase antibodies of the parents.

Does the metabolic syndrome exist in patients with type 1 diabetes?

Insulin resistance and many of the components of the metabolic syndrome *per se* have been implicated in the pathogenesis of micro- and macrovascular complications in type 1 diabetes. Thus, the question arises of whether these components cluster in patients with type 1 diabetes in a similar fashion as observed in subjects with the metabolic syndrome. If this is true, it would imply that the metabolic syndrome is not only a phenomenon associated with type 2 diabetes, but also with type 1 diabetes.

Interestingly, in Study III, the metabolic syndrome was shown to be a prevalent finding in patients with type 1 diabetes. The metabolic syndrome was observed in 38% of male and 40% of female patients. This was the first study to report the presence of the metabolic syndrome in patients with type 1 diabetes. The prevalence of the metabolic syndrome increased with age, being 33% in patients aged under 30 years and 47% in those over 50 years. These frequencies are clearly higher than in the general population in Finland, but lower than in patients with type 2 diabetes [16].

The metabolic syndrome was also more prevalent with worsening glycemic control and with worsening renal function. Importantly, the metabolic syndrome was associated with a 3.75-fold odds ratio for diabetic nephropathy after adjustment for traditional risk factors. In patients with type 2 diabetes, an association between the metabolic syndrome and diabetic nephropathy has also been reported. Isomaa *et al.* showed an association between the MS^{WHO} and both micro- and macrovascular complications [267]. It could be argued that this association would be influenced by the inclusion of albuminuria in the MS^{WHO}, but this does not seem to be the case since the association with complications has also been observed using MS^{IDF} and $MS^{AHA/NHLBI}$, neither of which includes microalbuminuria in the definition of the metabolic syndrome [330-332].

Of the components of the metabolic syndrome, hypertension appears to play a dominant role, an observation that is different from that seen in subjects without diabetes or with type 2 diabetes [16]. Nevertheless, all components of the metabolic syndrome were independently associated with diabetic nephropathy. Compared with patients fulfilling one or two components, each additional component further added to the odds ratio for diabetic nephropathy. This indicates that although hypertension might be important, each component play a role.

In Study III, the relationships between albuminuria and estimated renal function and between albuminuria and insulin sesnitivity was assessed. It seemed that the decline in insulin sensitivity was observed already in patients with microalbuminuria, well before the observed decline in renal function. This is in line with many previous studies reporting insulin resistance to precede or parallel the development of microalbuminuria and diabetic nephropathy in patients with type 1 diabetes [18,176,177], although

some contradictory studies also exist [178].

The role of the metabolic syndrome in patients with type 1 diabetes has since our original report been evaluated in several other studies summarized in Table 20. The Metascreen Study showed that the metabolic syndrome was a common finding in an Italian population of 638 patients with type 1 diabetes, who had a fairly high age at onset of type 1 diabetes [330]. The prevalence of the metabolic syndrome was 41% and 34% with the MS^{IDF} and $MS^{AHA/NHLBI}$ definitions, respectively, and was associated with a 3-fold odds ratio for diabetic nephropathy, which is similar to that observed in Study III. In our FinnDiane Study cohort, the MS^{NCEP} was also associated with low physical activity and independently associated with laser-treated retinopathy [333]. McGill *et al.* reported in a younger Australian cohort a significantly lower prevalence of the metabolic syndrome according to the MS^{WHO}, nevertheless, showing an association between the metabolic syndrome and diabetic complications, even in patients with a normal albumin excretion rate [320]. In a Hungarian population of similar age to the patients in Study III, the metabolic syndrome was observed in one-third of patients [334], and was further associated with a lower level of education [335].

In a recent study, presence of the metabolic syndrome in type 1 diabetes was compared with that observed in patients with type 2 diabetes, LADA, and subjects without diabetes. The metabolic syndrome was less common in patients with type 1 diabetes (32%), than in those with LADA (42%), although markedly more common in those with type 2 diabetes (89%). If glucose was excluded as a component of the metabolic syndrome, there was no excess of the metabolic syndrome in patients with type 1 diabetes compared with subjects without diabetes [336]. There were, however, rather large age differences between the different patient groups in this study. Taken together, in patients with type 1 diabetes, the metabolic syndrome is a common finding and is associated with micro- and macrovascular complications of diabetes. Thus, in answer to the question, the metabolic syndrome seems to exist also in patients with type 1 diabetes, although it is unclear whether the metabolic syndrome observed in type 1 diabetes is the same as in type 2 diabetes or in the general population.

MS^{IDF} identifies a similar proportion of patients as the MS^{NCEP}, although a greater gender difference is observed for MS^{IDF}, due to more stringent criteria for waist circumference [330,334]. In the general population, at least in the United States, such a gender difference between the two definitions has not been observed [337]. It is of note that in Study II an association between parental history of type 2 diabetes and the metabolic syndrome in patients with type 1 diabetes was also detected. This association has not been previously reported, although a German study found no association between type 2 diabetes in first-, or second-degree relatives and a modified metabolic syndrome in patients with type 1 diabetes [338].
[339]

Criticism against the existence of the metabolic syndrome

Recently, the whole concept of the metabolic syndrome has been challenged [340-342]. The main criticism does not question the clustering of cardiovascular risk factors, but making or not making the diagnosis of the metabolic syndrome. The usefulness of making the diagnosis with regard to clinical practice, research, or therapeutic aspects has been questioned. One argument has been that the current definitions for the metabolic syndrome do not include all potential components, but some factors like inflammatory markers and fatty liver has been left out. Criticism has also been raised because the components selected are not based on prospective follow-up studies, and the cut-off values are chosen arbitrarily. Those skeptical of the use of the metabolic syndrome further argue that the use of continuous variables would be more informative than the use of dichotomized

Table 20. Summary of publications regarding the metabolic syndrome in type 1 diabetes

Study	n	Mean age (years)	Diabetes duration (years)	MS (%)	MS M/F (%)	Definition	Findings
Cross-sectional							
Study III	2,415	37	22	39	38/40	NCEP	Association with nephropathy, renal function, CHD, age, and HbA_{1c}
Metascreen 2006 [330]	638	48	16	41 34	34/49 25/43	IDF AHA/NHLBI	Association with nephropathy, neuropathy, and CVD (IDF), but not retinopathy
Wadén 2007 (FinnDiane) [333]	1,028	36	21	30	28/31	NCEP	Association with lower levels of physical activity and diabetic retinopathy
McGill 2008 [320]	427	30	13	15	-	WHO	Association with micro- and macrovascular complications
Szadkowska 2008 [339]	165	~25	~17	11 11	- -	NCEP IDF	Association with body mass index, HbA_{1c}, age, and insulin dose
Nádas 2009 [334]	533	36	18	31 36	30/33 33/39	NCEP IDF	Prevalence estimate in Hungary.
Nádas 2009 [335]	437	38	19	35	32/37	NCEP	Association with lower level of education
Hawa 2009 [336]	288	44	18	32	-	NCEP	MS more prevalent in subjects with LADA and especially in patients with type 2 diabetes. If glucose was excluded as a component, MS was no more prevalent in type 1 diabetes than in conrol subjects without diabetes
Study II	1,860	43	27	40 40	- -	NCEP IDF	Association with parental type 2 diabetes
Prospective							
Davis 2007 [319]	127	42	11	45 42 39	- - -	WHO NCEP IDF	11-year follow-up, outcome death from cardiac cause (n=16). No predictive value of MS.
Kilpatrick 2007 [348]	1,337	27		22	13/32	IDF	No predictive value regarding micro- and macrovascular complications during follow-up
Pambianco 2007 [321]	514	27	19	21 12 8	28/14 13/11 2/14	WHO modified NCEP IDF	12-year follow-up. WHO best predictor, followed by NCEP and IDF. Components predicted better than overall syndrome.
Study IV	3,783	37	23	44 35 36	53/33 35/34 31/41	WHO NCEP IDF	5.5-year follow-up. WHO best predictor, followed by NCEP. IDF did not predict outcomes. MS predictor of CVD events and mortality, independent of albuminuria.

MS = metabolic syndrome, M = males, F = females, WHO = World Health Organization, NCEP = National Cholesterol Education Program Adult Treatment Panel III, IDF = International Diabetes Federation, AHA/NHLBI = American Heart Association/National Heart, Lung, and Blood Institute, CHD = coronary heart disease, CVD = cardiovascular disease, LADA = latent autoimmunity diabetes in adults.

variables. In addition, the use of the metabolic syndrome as a risk marker for cardiovascular disease beyond the risk associated with its individual components has been criticized. However, a confirmatory factor analysis supported the current clinical definition of the metabolic syndrome as well as the existence of a single factor underlying the metabolic syndrome and linking all of the components together [343]. Other confirmatory factor analyses have also suggested that a four-factor model including the current components of the syndrome (insulin resistance, obesity, lipids, and hypertension) would have the best fit, although not identifying an underlying factor [344]. Studies using principal component analysis have usually generated two to four components and found a weaker association with the core components and hypertension [345].

Those arguing for the existence of the metabolic syndrome highlight that these cardiovascular risk factors have been shown to cluster in several studies, ranging back more than a decade, and have repeatedly been associated with an increased cardiovascular risk [346]. In addition, although all components of the metabolic syndrome carry an individual risk of cardiovascular disease, the concept of a cluster of risk factors, the metabolic syndrome, serves as a simple and easily applicable tool in clinical practice to detect patients at risk of cardiovascular disease and also at risk of type 2 diabetes [347]. The decision to include some of the components in the syndrome, while omitting others, was made to ensure that the measurements are easily applicable in clinical practice worldwide, without making a statement that other components are less important in the pathogenesis of the syndrome [346]. Importantly, those in favor of the concept of the metabolic syndrome do not deny that the risk related to the syndrome is continuous in nature, and that the risk is higher the larger the waist circumference, the higher the blood pressure, the lower the HDL-cholesterol, the higher the triglyceride level, the more insulin resistant the individual, the more fat accumulation in the liver, and the higher the C-reactive protein concentration. Requiring three of the components of the metabolic syndrome for diagnosis does not mean that the risk is zero if two or less of the components are fulfilled or absolute if three or more components are fulfilled, but rather that the risk is continuous in nature. The more components, the greater the risk. And if one component is found, others should be sought.

Which of the current definitions is best in predicting cardiovascular risk in patients with type 1 diabetes?

In Study IV, the predictive role of the metabolic syndrome in cardiovascular events, cardiovascular and diabetes-related mortality, and progression of diabetic nephropathy was assessed. The results confirmed earlier findings regarding the metabolic syndrome as a predictor of cardiovascular disease and diabetes-related mortality in type 1 diabetes. It was evident that the different definitions identified different sets of patients, and thus, the predictive value of the definitions varied considerably. The MS^{WHO} was the strongest predictor, followed by the MS^{NCEP}, while the MS^{IDF} did not predict the studied outcomes at all. A new finding was that the MS^{WHO} was an independent predictor of cardiovascular events and cardiovascular and diabetes-related mortality, even after adjustment for diabetic nephropathy. It is noteworthy that the MS^{NCEP} added to the risk associated with elevated albuminuria alone.

The prevalence of the metabolic syndrome was similar using the different definitions, ranging from 35% to 44%, but only 18% fulfilled all three definitions. Since the different definitions did not necessarily identify the same patients, a comparison of the different definitions seems appropriate. In subjects without diabetes, the overlap between the different definitions is more complete. The MS^{NCEP} and the MS^{WHO} classify the subjects identically in 86% of cases [254], and MS^{NCEP} and MS^{IDF} in 93% of cases [337], while in Study IV the corresponding fre-

quencies were 75% and 73%.

The oldest of the three definitions, the MS^{WHO}, which is the only one that includes microalbuminuria, was associated with a 2.1-fold increased risk of cardiovascular events, and a 2.5-fold increased risk of cardiovascular and diabetes-related mortality after adjustment for diabetic nephropathy, and a 2.6-fold increased risk of progression to end-stage renal disease. The MS^{WHO} was also associated with a 2.8- and 3.1-fold increased risk of stroke and myocardial infarction, respectively, an association previously observed in subjects without diabetes [255]. The MS^{NCEP}, which gives equal importance to all components, was not an independent predictor after adjustment for diabetic nephropathy, although adjustment for traditional risk factors and previous events resulted in a 1.6-fold increased risk of cardiovascular events and a 2.2-fold increased risk of cardiovascular and diabetes-related mortality. Notably, these hazard ratios are of the same magnitude as in the general population. The MS^{IDF}, which highlights abdominal obesity as the central component, was not an independent predictor of the studied outcomes.

Our findings support the data from two prospective studies on the role of the metabolic syndrome in type 1 diabetes [321,348], and it is obvious that of the current definitions available the MS^{WHO} seems to be associated with the highest risk of cardiovascular outcomes. Results from the DCCT showed MS^{IDF} to be a poor predictor of micro- and macrovascular diabetic complications [348]. In their rather young patients, the prevalence of MS^{IDF} was the highest among those allocated to the intensively treated group. These same patients also gained the most weight, but had nevertheless the lowest risk of outcomes [144]. This could possibly explain the poor predictive value of the MS^{IDF} in the DCCT. In the Pittsburgh Epidemiology of Diabetes Complications Study, with generally younger patients and less diabetic complications than in Study IV, the prevalence of MS^{WHO}, MS^{NCEP}, and MS^{IDF} varied between 8% and 21%, and the MS^{WHO} was the best predictor of all outcomes studied, followed by the MS^{NCEP}, while the MS^{IDF} was again associated with the lowest risk [321]. The authors concluded that the individual components, especially albuminuria, which reflects generalized vascular damage and diabetic nephropathy, predicted the outcomes better than the metabolic syndrome itself. In Study IV, the MS^{WHO}, compared with the albuminuria component of the definition, showed a higher hazard ratio for cardiovascular events, but a lower hazard for cardiovascular and diabetes-related mortality. As shown in Study III, the prevalence of the metabolic syndrome increases with worsening renal disease in patients with type 1 diabetes, and diabetic nephropathy is also the strongest risk factor for cardiovascular outcomes in patients with type 1 diabetes [5]. In Study IV, most of the cardiovascular events were observed in those with diabetic nephropathy, and it is thus difficult to eliminate the effect of diabetic nephropathy. The independent risk shown for MS^{WHO} in cardiovascular events and cardiovascular and diabetes-related mortality adjusted for diabetic nephropathy suggests, however, that the metabolic syndrome indeed plays an independent role. Nevertheless, it could be argued that the observed effect is due to microalbuminuria, which is only included in the MS^{WHO} definition. This issue was therefore evaluated further, and an additional effect of the MS^{NCEP} beyond albuminuria alone was detected. This suggests a true role of the metabolic syndrome as a risk factor for cardiovascular outcomes and cardiovascular and diabetes-related mortality.

The metabolic syndrome is a predictor of chronic renal disease in the general population [14], but although MS^{NCEP} clearly increases in parallel with worsening of renal disease in patients with type 1 diabetes, the role of the metabolic syndrome as a risk factor for diabetic nephropathy is not straightforward. Results from the DCCT showed no effect of MS^{IDF} on the development of microalbuminuria, and in the Pittsburgh Epidemiology of Diabetes Complications Study, the MS^{IDF} had no effect on the development

of renal failure, while MS^{WHO} and MS^{NCEP} predicted renal failure. Interestingly, a recent large Chinese study in patients with type 2 diabetes showed MS^{NCEP} to increase the risk of chronic kidney disease in a 5-year follow-up [349]. In Study IV, only the MS^{WHO} predicted the development of microalbuminuria, while none of the definitions predicted progression from microalbuminuria to macroalbuminuria. At a later stage of the disease, both MS^{WHO} and MS^{NCEP} predicted progression from macroalbuminuria to end-stage renal disease. Taken together, the role of the metabolic syndrome in progression to microalbuminuria (incident microalbuminuria) is apparently modest, while at a later stage of the disease, multiple metabolic abnormalities increase the risk of chronic renal disease.

In patients with type 1 diabetes, abdominal obesity seems to be the component of the metabolic syndrome that has the weakest predictive role. This is a somewhat surprising finding since abdominal obesity is a key feature of insulin resistance, an established risk factor for cardiovascular disease [235]. All of the other individual components were, however, independent predictors of both cardiovascular events and cardiovascular and diabetes-related mortality. Although abdominal obesity was not independently associated with the outcomes, it could still play a role in the overall syndrome, for example, by being a contributing factor. The weak role of MS^{IDF}, which highlights obesity as the key feature, on the other hand indicates that obesity plays a minor role. In patients on dialysis, obesity has been associated with better survival (the obesity paradox), highlighting the importance of optimal nutrition in such patients [350]. In the present study, the MS^{IDF} obesity (waist circumference above 80 cm in females and 94 cm in males) was protective of development of end-stage renal disease, suggesting that the relationship between obesity and development of renal failure might be inverse or u-shaped, at least in patients with macroalbuminuria. In patients with type 1 diabetes, improvement of glycemic control could lead to an increase in body weight [351], and the protective role of obesity observed in Study IV could consequently be due to better glycemic control in these patients. In Study IV, the patients with macroalbuminuria who progressed to end-stage renal disease had, however, higher HbA_{1c} and lower insulin dose per body weight [352].

Concluding remarks and future prospects

Figure 14 summarizes the results of Studies I to IV and how the findings relate to each other. A strong association was present between the metabolic syndrome and diabetic nephropathy, but the predictive value of the metabolic syndrome in the development of diabetic nephropathy was less clear. The observed association between diabetic nephropathy and the cluster of parental risk factors suggests that a common underlying factor, for example insulin resistance, might be of greater importance than parental hypertension, cardiovascular disease, and diabetes in isolation. A genetic predisposition to insulin resistance could also explain the unfavorable metabolic profile seen in the patients with type 1 diabetes and the positive parental history of type 2 diabetes. It is noteworthy, that diabetic nephropathy and the metabolic syndrome (reflecting insulin resistance?) were both independent predictors of cardiovascular morbidity and mortality.

Studies I to IV left some questions unanswered, and further research is needed to assess the following questions: Do parental risk factors predict the development of diabetic nephropathy in prospective studies? What is the role of obesity in the progression of renal disease? Is there a true protective role of obesity in the progression to end-stage renal disease? If so, is the risk linear or u-shaped?

Another important question is whether the metabolic syndrome should be defined differently in patients with type 1 diabetes? And if so, should the main target be to find the best cardiovascular risk cluster? Or should it be to identify the best cluster that brings together and

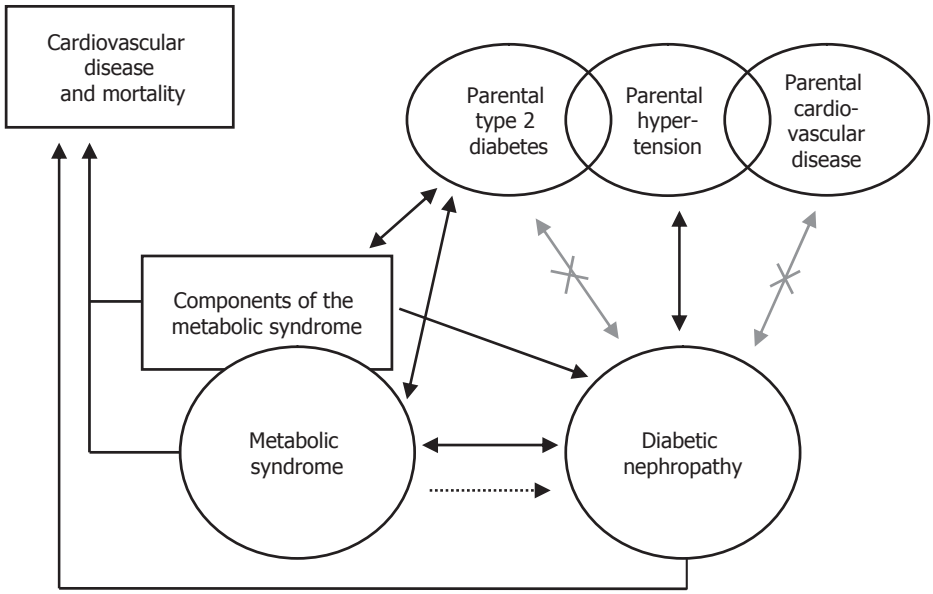


Figure 14. Summary of the findings of Studies I to IV.

highlights the pathogenetic mechanisms underlying the metabolic syndrome (insulin resistance, elevated triglycerides, low HDL-cholesterol, hypertension, abdominal obesity, inflammation, fatty liver)? Should a simple measure of insulin resistance, like the estimated glucose disposal rate or just the insulin dose, be added to the definition instead of hyperglycemia? It is also not known whether abdominal obesity should be defined differently. The MS^{IDF} includes abdominal obesity as a mandatory component, and it is important to acknowledge that all patients with insulin resistance are not obese [286]. Thus, requiring obesity in the definition might result in some subjects at risk being missed, as shown in the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe Study [353]. In addition, the cut-off value for waist circumference for females in the MS^{IDF} seems to lead to an overrepresentation of females with the metabolic syndrome in patients with type 1 diabetes, a phenomenon not observed in subjects without diabetes [337].

Another question is whether or not albuminuria should be included in the definition. In patients with diabetes, albuminuria usually reflects the presence of diabetic nephropathy (which seems to be an insulin resistant state), although the initial idea behind the inclusion of albuminuria in the definition was that it reflects a generalized vascular damage and endothelial dysfunction associated with insulin resistance.

Does recognition of the metabolic syndrome in patients with type 1 diabetes call for specific attention regarding their treatment? In the treatment, it is of course important to focus on diet, exercise, and weight loss, in addition to the use of cardio- and renoprotective agents to control blood pressure and dyslipidemia. Could oral hypoglycemic agents be beneficial in the treatment of overweight and insulin resistant patients with type 1 diabetes? One of the most frequently used oral hypoglycemic agents in overweight patients with type 2 diabetes is metformin, which enhances glycemic control through improvement of the actions of insulin in muscle and liver. The use of metformin is contraindicated in patients with kidney disease due to an increased risk of lactic acidosis. Some small-scale studies have used metformin as an adjunctive therapy in overweight patients with type 1 diabetes without diabetic nephropathy.

Improved glycemic control and insulin sensitivity as well as a decrease in daily insulin requirements without weight gain have been observed [354-359]. A newer class of oral hypoglycemic agents, the thiazolidinediones, also called insulin sensitizers, improve glycemic control in patients with type 2 diabetes, and have a beneficial effect on microvascular complications beyond their effect on glycemic control [181]. To date, only a few studies have investigated the use of thiazolidinediones in patients with type 1 diabetes. One study used rosiglitazone to treat 50 adult patients with type 1 diabetes and showed that the treatment was associated with a similar reduction in HbA_{1c} and a similar increase in weight as in the control group. In the treatment group, this was achieved with a smaller daily insulin dose, and the treatment further reduced blood pressure. The most pronounced effect of rosiglitazone was seen in patients with signs of insulin resistance [360]. By contrast, Zdravkovic *et al.* showed no beneficial effect of pioglitazone in 35 adolescents with type 1 diabetes. The treatment increased the body mass index, while a similar reduction in HbA_{1c} was seen in both the intervention and control groups [361]. Larger studies are needed to assess the safety and efficacy of both metformin and thiazolidinediones in patients with type 1 diabetes.

With the increasing epidemic of obesity worldwide, the presence of the metabolic syndrome will certainly also increase in patients with type 1 diabetes. This is a matter of great concern since insulin resistance, the components of the metabolic syndrome, and now also the metabolic syndrome itself are implicated in the pathogenesis of diabetic complications.

8 SUMMARY AND CONCLUSIONS

I Parental hypertension and type 1 diabetes, especially in the mothers, as well as paternal mortality, particularly from cardiovascular disease, were independently associated with diabetic nephropathy in patients with type 1 diabetes. Parental type 2 diabetes and cardiovascular disease were not independently associated with diabetic nephropathy, but a cluster of these two with parental hypertension was associated with diabetic nephropathy.

II Parental history of type 2 diabetes was associated with later onset of type 1 diabetes, a metabolic profile related to insulin resistance, and presence of the metabolic syndrome in patients with type 1 diabetes, despite similar HLA genotype distributions. No association emerged between parental history of type 2 diabetes and presence of hypertension or diabetic complications in these patients. Maternal history of type 2 diabetes seemed to be associated with a more unfavorable metabolic profile than paternal history of type 2 diabetes.

III The metabolic syndrome was prevalent in patients with type 1 diabetes, being observed in 38% of males and 40% of females. The prevalence of the metabolic syndrome increased with age, worsening of glycemic control, and worsening of renal disease. The metabolic syndrome was associated with 3.75-fold odds for diabetic nephropathy. The syndrome was further associated with a lower estimated glucose disposal rate, and a decline in insulin sensitivity was observed already in patients with microalbuminuria, well before apparent decline in renal function. This indicates that insulin resistance could precede the decline in renal function.

IV The different definitions of the metabolic syndrome, MS^{WHO}, MS^{NCEP}, and MS^{IDF}, did not necessarily identify the same patients. MS^{WHO}, which includes microalbuminuria in the definition, was the best predictor of cardiovascular morbidity and diabetes-related mortality, followed by MS^{NCEP}, while MS^{IDF} did not predict these outcomes. MS^{NCEP} added to the risk of cardiovascular morbidity, compared with albuminuria alone. Regarding the progression of renal disease, MS^{WHO} predicted progression to microalbuminuria, both MS^{WHO} and MS^{NCEP} predicted progression to end-stage renal disease, and M^{SIDF} surprisingly seemed protective.

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APPENDIX

The Finnish Diabetic Nephropathy Study Centers	
Anjalankoski Health Center	S.Koivula, T.Uggeldahl
Central Finland Central Hospital, Jyväskylä	T.Forslund, A.Halonen, A.Koistinen, P.Koskiaho, M.Laukkanen, J.Saltevo, M.Tiihonen
Central Hospital of Åland Islands, Mariehamn	M.Forsen, H.Granlund, A.-C.Jonsson, B.Nyroos
Central Hospital of Kanta-Häme, Hämeenlinna	P.Kinnunen, A.Orvola, T.Salonen, A.Vähänen
Central Hospital of Kymenlaakso, Kotka	R.Paldanius, M.Riihelä, L.Ryysy
Central Hospital of Länsi-Pohja, Kemi	H.Laukkanen, P.Nyländen, A.Sademies
Central Ostrobothnian Hospital District, Kokkola	S.Anderson, B.Asplund, U.Byskata, P.Liedes, M.Kuusela, T.Virkkala
City of Espoo Health Center:	
Espoonlahti	A.Nikkola, E.Ritola
Tapiola	M.Niska, H.Saarinen
Samaria	E.Oukko-Ruponen, T.Virtanen
Viherlaakso	A.Lyytinen
City of Helsinki Health Center:	
Puistola	H.Kari, T.Simonen
Suutarila	A.Kaprio, J.Kärkkäinen, B.Rantaeskola
Töölö	P.Kääriäinen, J.Haaga, A-L.Pietiläinen
City of Hyvinkää Health Center	S.Klemetti, T.Nyandoto, E.Rontu, S.Satuli-Autere
City of Vantaa Health Center:	
Korso	R.Toivonen, H.Virtanen
Länsimäki	R.Ahonen, M.Ivaska-Suomela, A.Jauhiainen
Martinlaakso	M.Laine, T.Pellonpää, R.Puranen
Myyrmäki	A.Airas, J.Laakso, K.Rautavaara
Rekola	M.Erola, E.Jatkola
Tikkurila	R.Lönnblad, A.Malm, J.Mäkelä, E.Rautamo
Heinola Health Center	P.Hentunen, J.Lagerstam
Helsinki University Central Hospital, Department of Medicine, Division of Nephrology	M.Feodoroff, L.Kyllönen, J.Kytö, S.Lindh, A.Sandelin, J.Tuomikangas, T.Vesisenaho
Herttoniemi Hospital, Helsinki	V.Sipilä
Hospital of Lounais-Häme, Forssa	T.Kalliomäki, J.Koskelainen, R.Nikkanen, N.Savolainen, H.Sulonen, E.Valtonen
Iisalmi Hospital	E.Toivanen
Jokilaakso Hospital, Jämsä	A.Parta, I.Pirttiniemi
Jorvi Hospital, Helsinki University Central Hospital	S.Aranko, S.Ervasti, R.Kauppinen-Mäkelin, A.Kuusisto, T.Leppälä, K.Nikkilä, L.Pekkonen
Jyväskylä Health Center, Kyllö	K.Nuorva, M.Tiihonen
Kainuu Central Hospital, Kajaani	S.Jokelainen, P.Kemppainen, A-M.Mankinen, M.Sankari
Kerava Health Center	H.Stuckey, P.Suominen
Kirkkonummi Health Center	A.Lappalainen, M.Liimatainen, J.Santaholma
Kivelä Hospital, Helsinki	A.Aimolahti, E.Huovinen
Koskela Hospital, Helsinki	V.Ilkka, M.Lehtimäki
Kotka Health Center	E.Pälikkö-Kontinen, A.Vanhanen
Kouvola Health Center	E.Koskinen, T.Siitonen
Kuopio University Hospital	E.Huttunen, R.Ikäheimo, P.Karhapää, P.Kekäläinen, M.Laakso, T.Lakka, E.Lampainen, L.Moilanen, L.Niskanen, U.Tuovinen, I.Vauhkonen, E.Voutilainen

Kuusamo Health Center	T.Kääriäinen, E.Isopoussu
Kuusankoski Hospital	E.Kilkki, I.Koskinen, L.Riihelä
Laakso Hospital, Helsinki	T.Meriläinen, P.Poukka, R.Savolainen, N.Uhlenius
Lahti City Hospital	A.Mäkelä, M.Tanner
Lapland Central Hospital, Rovaniemi	L.Hyvärinen, S.Severinkangas, T.Tulokas
Lappeenranta Health Center	P.Linkola, I.Pulli
Lohja Hospital	T.Granlund, M.Saari, T.Salonen
Länsi-Uusimaa Hospital, Tammisaari	I.-M.Jousmaa, J.Rinne
Loimaa Health Center	A.Mäkelä, P.Eloranta
Malmi Hospital, Helsinki	H.Lanki, S.Moilanen, M.Tilly-Kiesi
Mikkeli Central Hospital	A.Gynther, R.Manninen, P.Nironen, M.Salminen, T.Vänttinen
Mänttä Regional Hospital	I.Pirttiniemi, A-M.Hänninen
North Karelian Hospital, Joensuu	U-M.Henttula, P.Kekäläinen, M.Pietarinen, A.Rissanen, M.Voutilainen
Nurmijärvi Health Center	A.Burgos, K.Urtamo
Oulaskangas Hospital, Oulainen	E.Jokelainen, P.-L.Jylkkä, E.Kaarlela, J.Vuolaspuro
Oulu Health Center	L.Hiltunen, R.Häkkinen, S.Keinänen-Kiukaanniemi
Oulu University Hospital	R.Ikäheimo
Päijät-Häme Central Hospital	H.Haapamäki, A.Helanterä, S.Hämäläinen, V.Ilvesmäki, H.Miettinen
Palokka Health Center	P.Sopanen, L.Welling
Pieksämäki Hospital	V.Javtsenko, M.Tamminen
Pietarsaari Hospital	M-L.Holmbäck, B.Isomaa, L.Sarelin
Pori City Hospital	P.Ahonen, P.Merensalo, K.Sävelä
Porvoo Hospital	M.Kallio, B.Rask, S.Rämö
Raahe Hospital	A.Holma, M.Honkala, A.Tuomivaara, R.Vainionpää
Rauma Hospital	K.Laine, K.Saarinen, T.Salminen
Riihimäki Hospital	P.Aalto, E.Immonen, L.Juurinen
Salo Hospital	A.Alanko, J.Lapinleimu, P.Rautio, M.Virtanen
Satakunta Central Hospital, Pori	M.Asola, M.Juhola, P.Kunelius, M.-L.Lahdenmäki, P.Pääkkönen, M.Rautavirta
Savonlinna Central Hospital	T.Pulli, P.Sallinen, M.Taskinen, E.Tolvanen, H.Valtonen, A.Vartia
Seinäjoki Central Hospital	E.Korpi-Hyövälti, T.Latvala, E.Leijala
South Karelia Central Hospital, Lappeenranta	T.Ensala, E.Hussi, R.Härkönen, U.Nyholm, J.Toivanen
Tampere Health Center	A.Vaden, P.Alarotu, E.Kujansuu, H.Kirkkopelto-Jokinen, M.Helin, S.Gummerus, L.Calonius, T.Niskanen, T.Kaitala, T.Vatanen
Tampere University Hospital	I.Ala-Houhala, T.Kuningas, P.Lampinen, M.Määttä, H.Oksala, T.Oksanen, K.Salonen, H.Tauriainen, S.Tulokas
Tiirismaa Health Center, Hollola	T.Kivelä, L.Petlin, L.Savolainen
Turku Health Center	I.Hämäläinen, H.Virtamo, M.Vähätalo
Turku University Central Hospital	K.Breitholz, R.Eskola, K.Metsärinne, U.Pietilä, P.Saarinen, R.Tuominen, S.Äyräpää
Vaajakoski Health Center	K.Mäkinen, P.Sopanen
Valkeakoski Regional Hospital	S.Ojanen, E.Valtonen, H.Ylönen, M.Rautiainen, T.Immonen
Vammala Regional Hospital	I.Isomäki, R.Kroneld, M.Tapiolinna-Mäkelä
Vasa Central Hospital	S.Bergkulla, U.Hautamäki, V.-A.Myllyniemi, I.Rusk

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